

I. SYNTHESIS OF INDOLINES AND INDOLES VIA INTRAMOLECULAR [4 + 2]
CYCLOADDITION OF YNAMIDES AND CONJUGATED ENYNES

II. SYNTHESIS OF NITROGEN HETEROCYCLES IN SUPERCRITICAL
CARBON DIOXIDE

by

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B. A., Chemistry
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SUBMITTED TO THE DEPARTMENT OF CHEMISTRY
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FOR THE DEGREE OF

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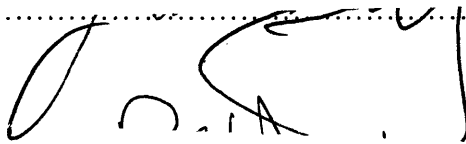
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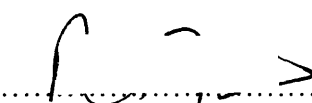


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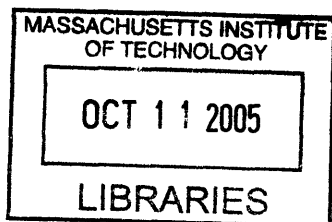
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ABSTRACT

A general amination strategy for the N-alkynylation of carbamates, sulfonamides, and chiral oxazolidinones and imidazolidinones is described. A variety of substituted ynamides are available by deprotonation of amide derivatives with KHMDS followed by reaction with CuI and an alkynyl halide.

Ynamides react with conjugated enynes in intramolecular [4 + 2] cycloaddition to afford substituted indolines that undergo oxidation with *o*-chloranil to furnish the corresponding indoles. The cycloaddition substrates are easily assembled from derivatives of 3-butynylamine by Sonogashira coupling with alkenyl halides followed by copper-catalyzed N-alkynylation with acetylenic bromides. Diynamides participate as particularly reactive 2π components in the cycloaddition, providing access to indolines with carbon substituents at the C-7 position. Enynamides serve as 4π components in a complementary version of the cycloaddition strategy which provides access to indoles and indolines substituted with substituents at C-4. These enyne cycloadditions take place upon heating the substrates at 110–210 °C in toluene or 2,2,2-trifluoroethanol and in some cases can be achieved at 0 °C to room temperature in the presence of Lewis acids such as Me₂AlCl.

We have developed a “green” strategy to effect acyl-Pictet-Spengler reactions in multiphasic scCO₂/CO₂-expanded liquid media. These cyclizations of iminium ions provide tetrahydroisoquinolines and tetrahydro- β -carboline derivatives that have valuable medicinal properties. Critical to the success of these reactions is the in situ conversion of β -arylethylamine reactants to carbamate derivatives by reaction with carbon dioxide and dialkyl carbonates. The application of this general strategy for utilizing amines in other carbon-nitrogen bond-forming reactions in environmentally-friendly media is under investigation.

Thesis Supervisor: Rick L. Danheiser

Title: Professor of Chemistry

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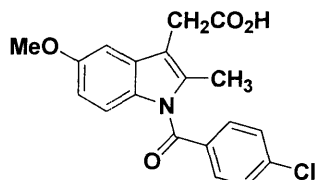
Part I

Synthesis of Indolines and Indoles via Intramolecular [4 + 2] Cycloaddition of Ynamides and Conjugated Enynes

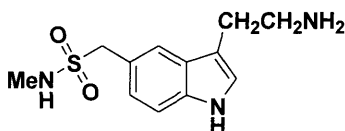
Chapter 1

Strategies for the Synthesis of Indoles and Indolines

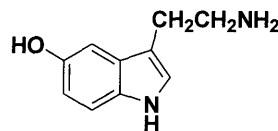
Indoles! Chemical research has focused on the synthesis of indoles and their derivatives for well over a century.^{1,2} These important heterocycles are key structural features in numerous natural products and synthetic targets of biological and commercial interest. Chemists originally applied indoles and their derivatives as dyes for textiles, and in more recent years scientists have focused their attention on the wide range of biological activity exhibited by these compounds. Many indoles and related indolines have medicinal properties that guide the direction of pharmaceutical drug design. For example, indomethacin (**1**) is an anti-inflammatory agent and sumatriptan (**2**) mitigates the pain of migraine headaches. Other important examples of indoles and indolines that exhibit biological activity are shown below.



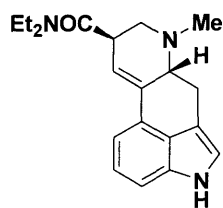
indomethacin (**1**)



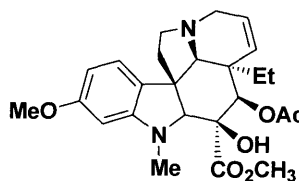
sumatriptan (**2**)



serotonin (**3**)



lysergic acid
diethylamide (**4**)



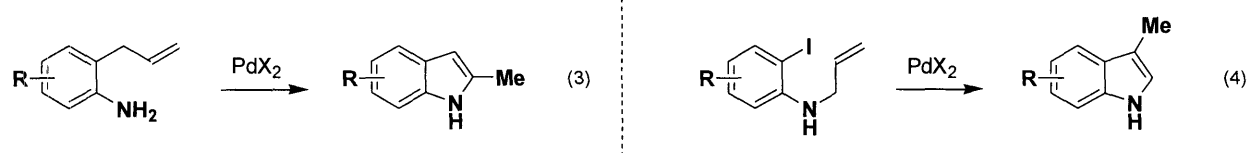
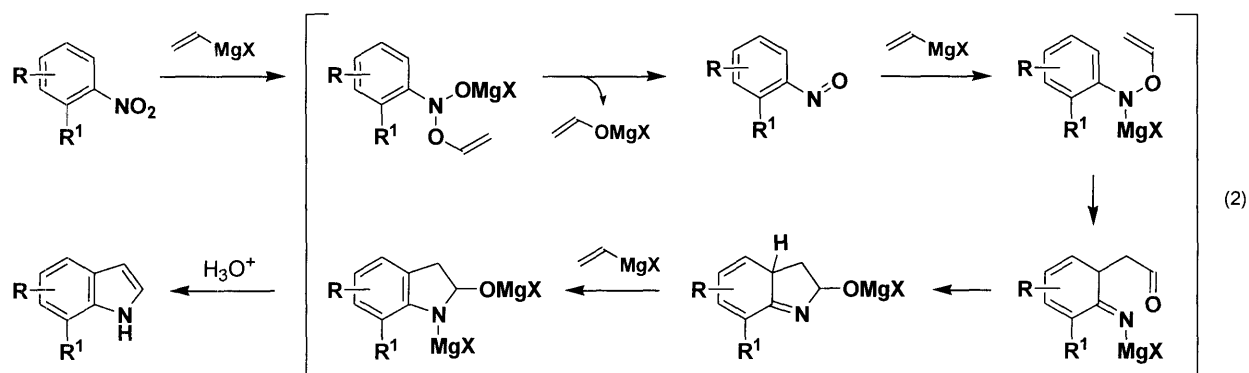
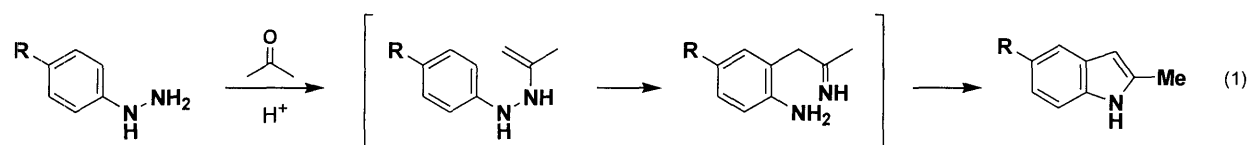
vindoline (**5**)

Chemists are motivated to explore new methods for the efficient synthesis of indoles and related structures found in drug targets. The most common strategies for the synthesis of these

¹ (a) Joule, J. A. In *Science of Synthesis*; Thomas, E. J., Ed.; Thieme: Stuttgart, 2000; Vol. 10, pp 361–652. (b) Sundberg, R. J. *Indoles*; Academic Press: London, 1996.

² For recent reviews of indole syntheses, see: (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (b) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. (c) Gribble, G. W. *Contemp. Org. Synth.* **1994**, 145.

heterocycles involve the assembly of the pyrrole ring from preformed benzene precursors.^{1,2} The venerable Fischer indole synthesis³ showcases this type of strategy by constructing the five-membered ring of the indole from an arylhydrazine (eq 1). More recently discovered methods that involve the annulation of the pyrrole ring onto benzene precursors include the Bartoli indole synthesis⁴ (eq 2) and the powerful palladium-catalyzed cyclizations pioneered by Hegedus,⁵ Ban,⁶ and Heck⁷ (eq 3–4).



Functionalization of the indole benzenoid ring via electrophilic aromatic substitution or metalation followed by treatment with electrophiles is often difficult due to competitive reactions at the pyrrole ring. As a result, strategies for indole synthesis involving annulation of the five-membered ring onto benzene derivatives generally rely on the availability of substituted benzene precursors for the construction of indoles that are highly functionalized on the *six-membered*

³ Robinson, B. *The Fischer Indole Synthesis*; Wiley-Interscience: New York, 1982.

⁴ Bartoli, G.; Palmieri, G.; Bosco, M.; Dalpozzo, R. *Tetrahedron Lett.* **1989**, 30, 2129.

⁵ For seminal publication, see: Hegedus, L. S.; Allen, G. F.; Waterman, E. L. *J. Am. Chem. Soc.* **1976**, 98, 2674.

⁶ For seminal publication, see: Mori, M.; Chiba, K.; Ban, Y. *Tetrahedron Lett.* **1977**, 18, 1037.

⁷ For seminal publication, see: Terpkow, M. O.; Heck, R. F. *J. Am. Chem. Soc.* **1979**, 101, 5281.

Intramolecular cycloaddition strategies are powerful vehicles for the direct assembly of the bicyclic indole ring system from acyclic precursors. These convergent approaches form multiple bonds and rings in one step, and substituents embedded within acyclic substrates are incorporated in the bicyclic system after cycloaddition. As a result, these strategies allow for the synthesis of indoles and indolines with regiocontrolled access to substitution on the six-membered ring.

Scheme 1

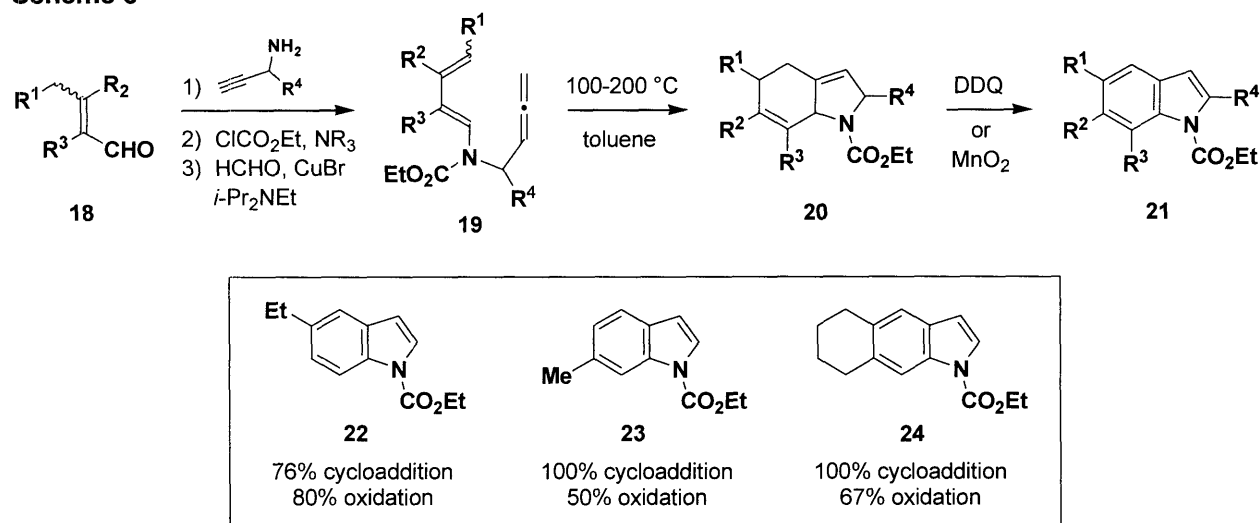


13

reported the [4 + 2] cycloaddition of diazines onto internal allenes as a route to indoles (Scheme 2).⁹ These thermally-promoted reactions proceed at high temperatures to provide indolines and indoles with regiocontrol over substitution on the benzenoid ring.¹⁰ While some diazines such as **6** are commercially available, more substituted diazines such as **12** require assembly via intermolecular [4 + 2] cycloadditions of tetrazines and enamines (or enol ethers). In addition, the nucleophilic aromatic substitution of unsymmetrical diazines by amines leads to mixtures of aminodiazines.

In 1986, Kanematsu published a new indole synthesis involving the intramolecular [4 + 2] cycloaddition of dienamides and allenes (Scheme 3).¹¹ The cycloaddition of dienamide-allene substrates generates bicyclic tetrahydroindole systems and subsequent oxidation provides indoles with various substitution patterns on the six-membered ring. As shown below, treatment of α,β -unsaturated imines with ethyl chloroformate provides the requisite dienamides, and homologation of the acetylenes to allenes installs the 2π component. These cycloadditions generally proceed in good-to-excellent yields, and the oxidation of cycloadducts with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or manganese dioxide provides indoles.

Scheme 3



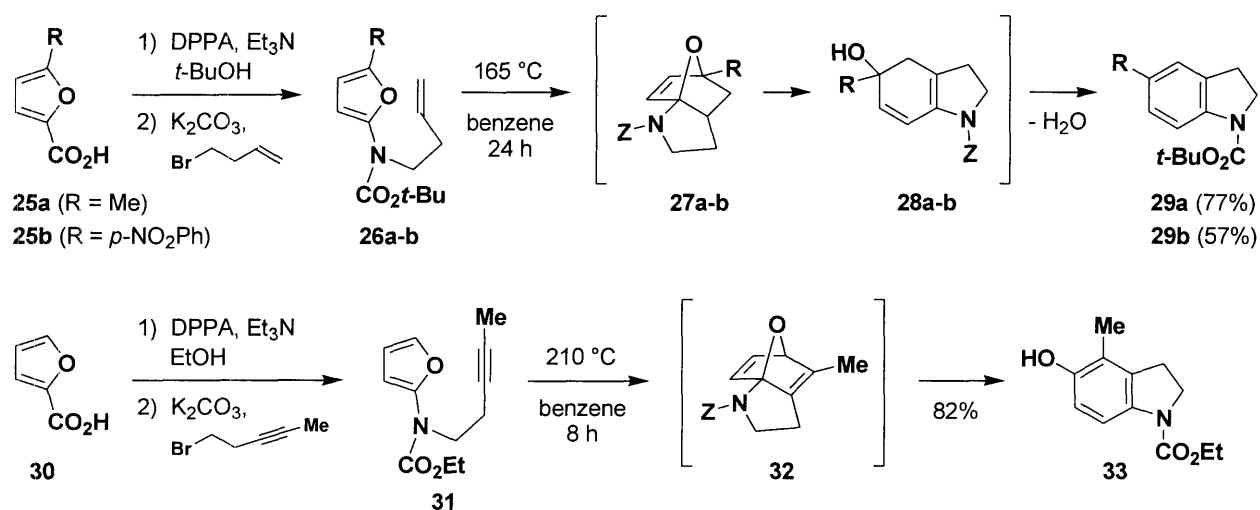
⁹ Boger, D. L.; Sakya, S. M. *J. Org. Chem.* **1988**, *53*, 1415.

¹⁰ For applications in total synthesis, see: (a) Boger, D. L.; Coleman, R. S. *J. Org. Chem.* **1986**, *51*, 3250. (b) Boger, D. L.; Coleman, R. S.; Invergo, B. J. *J. Org. Chem.* **1987**, *52*, 1521. (c) Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.* **1987**, *109*, 2717. (d) Boger, D. L.; Zhang, M. *J. Am. Chem. Soc.* **1991**, *113*, 4230. (e) Boger, D. L.; Wolkenberg, S. E. *J. Org. Chem.* **2000**, *65*, 9120.

¹¹ Hayakawa, K.; Yasukouchi, T.; Kanematsu, K. *Tetrahedron Lett.* **1986**, *27*, 1837.

In 1999, Padwa reported the intramolecular [4 + 2] cycloaddition of furans with tethered alkenes or alkynes as a route to substituted indolines (Scheme 4).^{12,13} These thermal cycloadditions provide indolines in good yields, and substrates such as **26** and **31** are available in two steps from 2-furoic acids. The synthesis of highly substituted indolines, however, is limited by the availability of substituted furanyl precursors which are not always trivial to prepare.¹⁴ Padwa has demonstrated the utility of his cycloaddition strategy by its application in the synthesis of dendrobine^{15a,b} and stenine^{15c} and studies directed toward other alkaloid natural products.^{15d-f}

Scheme 4



During the course of our studies, Witulski reported another strategy for the synthesis of indolines involving the intramolecular [4 + 2] cycloaddition of dienes with ynamides (Scheme 5).¹⁶ These thermal or transition-metal-catalyzed cycloadditions produce dihydroindolines, and

¹² Padwa, A.; Brodney, M. A.; Liu, B.; Satake, K.; Wu, T. *J. Org. Chem.* **1999**, *64*, 3595.

¹³ For subsequent studies, see: (a) Padwa, A.; Brodney, M. A.; Satake, K.; Straub, C. S. *J. Org. Chem.* **1999**, *64*, 4617. (b) Bur, S. K.; Lynch, S. M.; Padwa, A. *Org. Lett.* **2002**, *4*, 473. (c) Padwa, A.; Ginn, J. D.; Bur, S. K.; Eidell, C. K.; Lynch, S. M. *J. Org. Chem.* **2002**, *67*, 3412. (d) Bur, S. K.; Padwa, A. *Org. Lett.* **2002**, *4*, 4135.

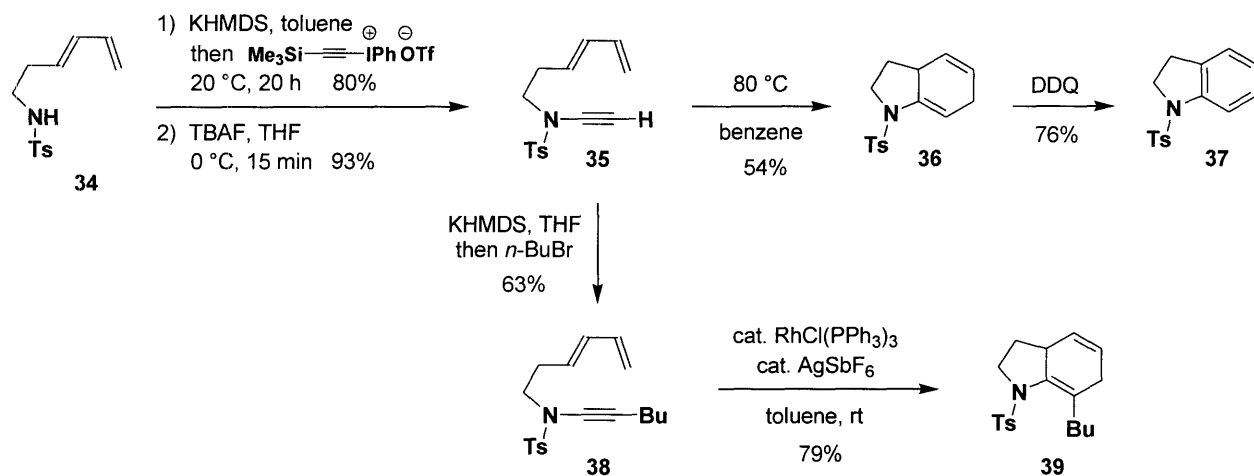
¹⁴ For the preparation of requisite 2-aminofurans, see: (a) Rashatasakhon, P.; Padwa, A. *Org. Lett.* **2003**, *5*, 189. (b) Padwa, A.; Crawford, K. R.; Rashatasakhon, P.; Rose, M. *J. Org. Chem.* **2003**, *68*, 2609. (c) Padwa, A.; Rashatasakhon, P.; Rose, M. *J. Org. Chem.* **2003**, *68*, 5139.

¹⁵ (a) Padwa, A.; Dimitroff, M.; Liu, B. *Org. Lett.* **2000**, *2*, 3233. (b) Padwa, A.; Brodney, M. A.; Dimitroff, M.; Liu, B.; Wu, T. *J. Org. Chem.* **2001**, *66*, 3119. (c) Ginn, J. D.; Padwa, A. *Org. Lett.* **2002**, *4*, 1515. (d) Lynch, S. M.; Bur, S. K.; Padwa, A. *Org. Lett.* **2002**, *4*, 4643. (e) Padwa, A.; Brodney, M. A.; Lynch, S. M.; Rashatasakhon, P.; Wang, Q.; Zhang, H. *J. Org. Chem.* **2004**, *69*, 3735. (f) Padwa, A.; Bur, S. K.; Zhang, H. *J. Org. Chem.* **2005**, ASAP.

¹⁶ Witulski, B.; Lumtscher, J.; Bergsträsser, U. *Synlett* **2003**, 708.

subsequent oxidation of the cycloadducts affords the indoline. The ynamides in this study were generated from the reaction of metalated sulfonamides with alkynyl(phenyl)iodonium salts, which is an important method for ynamide synthesis that is discussed in greater detail in Chapter 3 of this thesis. Witulski found that the terminal ynamide **35** was the only substrate able to undergo cycloaddition under thermal conditions, whereas transition-metals catalyzed the cycloadditions of several other ynamides bearing substitution on the acetylene. Witulski did not explore the scope of this reaction with regard to substitution on the diene, although in principle cycloadditions involving more highly substituted dienes could furnish indolines with greater degrees of substitution on the six-membered ring. In practice, however, it might often be more difficult to access more highly substituted diene precursors, and problems could arise in the dehydrogenation of the cycloadducts (i.e., corresponding to **36** and **39**) bearing substituents on the six-membered ring.

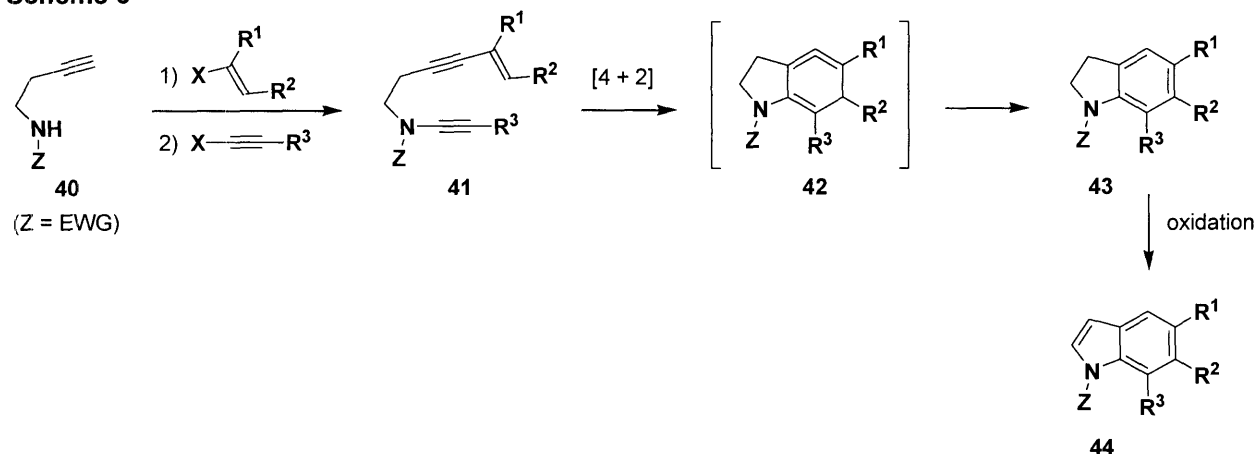
Scheme 5



The important cycloaddition strategies of Boger, Kanematsu, Padwa, and Witulski all generate the bicyclic indole (or indoline) skeleton in a single step from acyclic substrates. Their application to the preparation of substituted indoles and indolines, however, requires precursor diazines, dienes, and furans with substitution that in some cases may not be straightforward to access. In the case of more highly substituted targets, problems can also arise in the steps necessary to convert the initial cycloadducts to the aromatic indoles. As a result, these cycloaddition strategies may not be suitable for the general synthesis of indoles and indolines that are highly substituted on the benzenoid ring.

The first part of this thesis describes our development of the intramolecular [4 + 2] cycloaddition of ynamides with conjugated enynes (Scheme 6) as a method for the synthesis of indolines and indoles that are highly substituted on the six-membered ring. In the proposed reaction, the initial cycloaddition of **41** would generate a highly strained isoaromatic cyclic allene **42** that should rearrange to indoline **43** via proton or hydrogen atom transfer pathways that will be discussed in the next chapter. Oxidation of the indoline products would then afford indoles. The cycloaddition substrates should be available from simple derivatives of 3-butyne-1-amine via a sequence of transition-metal-mediated coupling reactions. Sonogashira coupling of **40** with an alkenyl halide or sulfonate would generate the requisite enyne moieties with a variety of substitution patterns, and subsequent alkynylation of the nitrogen would then install the ynamide. The cycloaddition of **41** and oxidation of **43** would provide indolines and indoles with multiple substituents on the six-membered ring, and we anticipated that this highly modular approach would be especially well-suited for the preparation of libraries of substituted indole derivatives. Our investigation of enyne cycloadditions as a strategy for synthesizing aromatic and heteroaromatic systems will be discussed in detail in the next chapter.

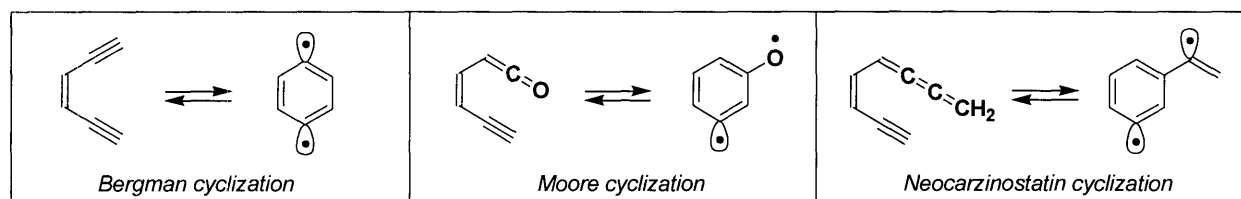
Scheme 6



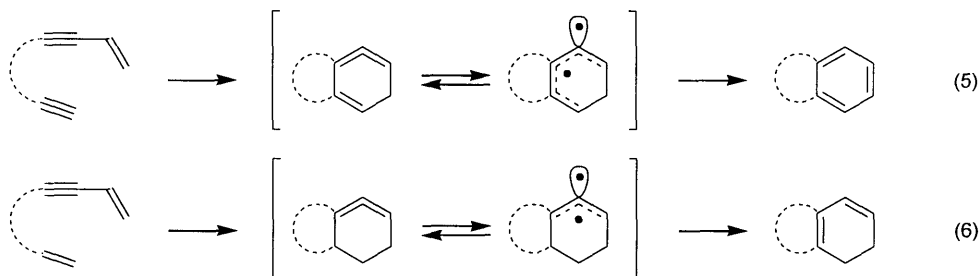
Chapter 2

[4 + 2] Cycloadditions of Conjugated Enynes

Cycloadditions are powerful synthetic tools for the rapid assembly of complex cyclic compounds.¹⁷ The utility of these reactions in organic synthesis is proven by their widespread use in the preparation of natural products and commercially important organic compounds. Intramolecular cycloadditions often provide convergent approaches to the synthesis of polycyclic compounds in which multiple bonds and rings are formed in one step. In seeking inspiration for the design of new cycloaddition strategies, our attention was drawn to cycloaromatizations¹⁸ such as the Bergman, Myers, and Moore cyclizations. These unimolecular reactions of highly



unsaturated conjugated systems generate benzene rings via strained and/or high-energy intermediates. We have focused our attention on designing new *cycloaddition* reactions that would also provide aromatic rings from highly unsaturated precursors. For example, we were interested in exploring the transformations outlined below in which a conjugated enyne combines with an alkyne or alkene in a [4 + 2] cycloaddition to form a highly strained cyclic allene (or



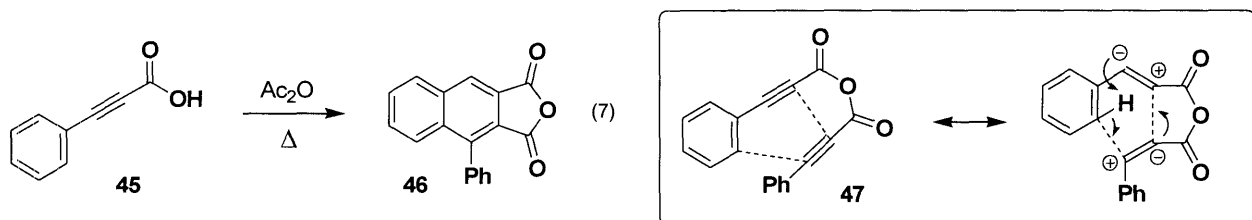
¹⁷ Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: New York, 1990.

¹⁸ For reviews on cycloaromatizations, see: (a) Maier, M. E. *Synlett* **1995**, 13. (b) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem. Int. Ed.* **1991**, 30, 1387.

biradical) which would rearrange to afford aromatic or dihydroaromatic products. If these processes proved to be general and efficient, it occurred to us these cycloadditions could provide a powerful strategy for the synthesis of a wide range of carbocyclic and heterocyclic systems.

Although the transformations in eq 5–6 might proceed via highly strained cyclic allene intermediates, we viewed these processes as feasible for several reasons. First, we estimated the enthalpy of reaction for this transformation to be -29.7 kcal/mol,¹⁹ wherein the exothermicity of this process likely benefits from the highly favorable conversion of two relatively weak acetylenic π bonds into two new carbon-carbon σ bonds. Similarly, Johnson has reported ab initio calculations that predict a value of -25.4 kcal/mol for the enthalpy change for the cycloaddition.²⁰ In addition, calculations by Ananikov predict a change in Gibbs free energy of -29.8 kcal/mol for the conversion of 1-buten-3-yne and ethyne to 1,2,4-cyclohexatriene.²¹

Also encouraging with regard to the feasibility of these transformations was the fact that scattered reports have appeared in the literature describing reactions related to these enyne cycloadditions. Arenyne cycloadditions, in which the alkene component of the enyne is embedded in an aromatic ring, were observed as early as 1898 when Michael and Bucher obtained naphthalene **46** unexpectedly upon heating phenylpropionic acid in refluxing acetic anhydride.²² The nature of this reaction, however, was not understood by Michael and Bucher, and later Baddar proposed that this reaction involves the intermediacy of anhydride **47** which undergoes “cyclization” via the zwitterionic species shown below.^{23,24}



¹⁹ Estimated using the Benson group additivity method (Benson, S. W. *Thermochemical Kinetics*; Wiley: New York, 1976) and the heat of formation for 1,2,4-cyclohexatriene (93.7 kcal/mol) reported by Janoschek, R. *Angew. Chem. Int. Ed.* **1992**, 31, 476.

²⁰ Burrell, R. C.; Daoust, K. J.; Bradley, A. Z.; DiRico, K. J.; Johnson, R. P. *J. Am. Chem. Soc.* **1996**, 118, 4218.

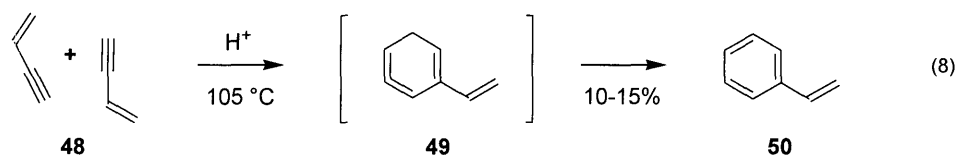
²¹ Ananikov, V. P. *J. Phys. Org. Chem.* **2001**, 14, 109.

²² Michael, A.; Bucher, J. E. *Am. Chem. J.* **1898**, 20, 89.

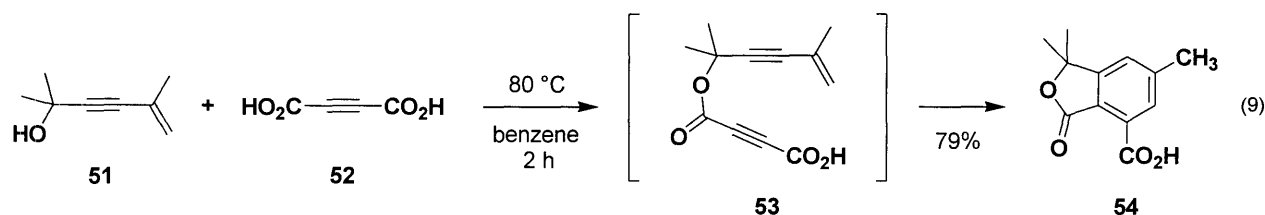
²³ Baddar, F. G.; El-Assal, L. S. *J. Chem. Soc.* **1948**, 1267.

²⁴ For reviews of early investigations into the “Michael-Bucher” reaction, see: (a) Onishchenko, A. S. *Diene Synthesis*; Israel Program for Scientific Translations: Jerusalem, 1964; pp 249-254, 635-637. (b) Vartanyan, S. A. *Russ. Chem. Rev.* **1962**, 31, 529. (c) Viehe, H. G. *Chemistry of Acetylenes*; Marcel Dekker: New York, 1969; pp 494-496. (d) Johnson, A. W. *The Chemistry of the Acetylenic Compounds*; Langmans, Green, and Co.: New York, 1950; pp 6-9. For recent intramolecular arenynene cycloadditions, see: (e) Rodríguez, D.; Martínez-Espérón, M. F.; Navarro-Vázquez, A.; Castedo, L.; Domínguez, D.; Saá, C. *J. Org. Chem.* **2004**, 69, 3842 and references therein.

To our knowledge, Dykstra reported the first cycloadditions of conjugated *enynes* in 1934 in connection with his study of the polymerization of vinylacetylenes.²⁵ Heating enyne **48** with protic additives (1–10% by volume) such as acetic acid, benzoic acid, hydrogen chloride, or methanol produced styrene in low yield, and Dykstra proposed the reaction proceeds by way of cyclic allene intermediate **49**. Dykstra also commented, however, that **49** appears to be “practically impossible stereochemically” and suggested a concomitant cycloaddition and isomerization to afford styrene products directly. Since this initial report by Dykstra, several other scattered examples of intermolecular [4 + 2] cycloadditions of conjugated enynes have appeared in the literature.²⁶



In 1945, Johnson reported the first example of an *intramolecular* [4 + 2] cycloaddition involving a conjugated enyne.²⁷ Johnson proposed that the formation of phthalide **54** proceeds via thermal cycloaddition of intermediate **53**. Later studies by Hakopian demonstrated that the



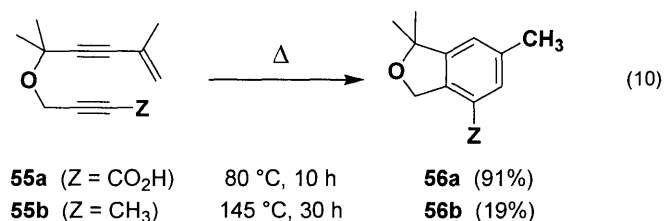
rate and efficiency of thermal intramolecular enyne cycloadditions increase when the 2π component, or “enynophile”, is activated by an electron-withdrawing group (eq 10).²⁸

²⁵ Dykstra, H. B. *J. Am. Chem. Soc.* **1934**, 56, 1625.

²⁶ (a) Dané, E.; Höss, O.; Bindsell, A. W.; Schmitt, J. *Liebigs. Ann.* **1937**, 532, 39. (b) Dané, E.; Höss, O.; Eder, K.; Schmitt, J.; Schön, O. *Liebigs. Ann.* **1938**, 536, 183. (c) Butz, L. W.; Gaddis, A. M.; Butz, E. W. J.; Davis, R. E. *J. Org. Chem.* **1940**, 5, 379. (d) Ray, F. E.; Sawicki, E.; Borum, O. H. *J. Am. Chem. Soc.* **1952**, 74, 1247. (e) Israelashvili, S.; Edlitz-Pfeffermann, J. *J. Am. Chem. Soc.* **1952**, 74, 5780. (f) Nekipelova, T.D.; Fentsov, D. V. *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1989**, 38, 1885. (g) Miller, B.; Ionescu, D. *Tetrahedron Lett.* **1994**, 35, 6615.

²⁷ Johnson, A. W. *J. Chem. Soc.* **1945**, 715.

²⁸ (a) Hakopian, L. A.; Gezalian, G. I.; Grigorian, S. G.; Matsoyan, S. G. *Arm. Khim. Zh.* **1974**, 27, 764. (b) Hakopian, L. A.; Gezalian, G. I.; Matsoyan, S. G. *Arm. Khim. Zh.* **1974**, 27, 768. (c) Hakopian, L. A.; Gezalian, G. I.; Matsoyan, S. G. *Arm. Khim. Zh.* **1975**, 28, 72.



Scope of Intramolecular [4 + 2] Cycloadditions of Conjugated Enynes

Despite a few other scattered reports²⁹ in the literature describing intramolecular [4 + 2] cycloadditions of conjugated enynes, the generality and scope of this fascinating reaction remained undefined until our laboratory began to systematically investigate this transformation as an efficient route to highly substituted aromatic and heteroaromatic compounds. In 1994, our laboratory reported on studies that established the feasibility of these cycloadditions as a practical method for organic synthesis and discussed possible mechanisms for these reactions.³⁰ This study demonstrated that reaction substrates are simple to prepare and that substituents incorporated into the enyne and enynophile allow for regiocontrol over substitution on aromatic products. Subsequent work in our laboratory has investigated the degree to which the rate and efficiency of cycloaddition are affected by variations in substitution on the enyne, functionality on the enynophile, and the nature of the linking tether.^{31,32,33,34} Representative examples from previous studies in our laboratory are shown in Table 1.

²⁹ For other scattered reports of early intramolecular enyne cycloadditions, see: (a) Nazarov, I. N.; Verkholetova, G. P.; Torgov, I. V. *J. Gen. Chem. USSR (Engl. Transl.)* **1959**, 29, 3277. (b) Hoffmann, H. M. R.; Krumwiede, D.; Mucha, B.; Oehlerking, H. H.; Prahst, G. W. *Tetrahedron* **1993**, 49, 8999. For examples after our preliminary communication, see: (c) González, J. J.; Francesch, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Org. Chem.* **1998**, 63, 2854. (d) Rodríguez, D.; Castedo, L.; Domínguez, D.; Saá, C. *Org. Lett.* **2003**, 5, 3119. (e) Martínez-Esperón, M. F.; Rodríguez, D.; Castedo, L.; Saá, C. *Org. Lett.* **2005**, 7, 2213.

³⁰ Danheiser, R. L.; Gould, A. E.; Fernández de la Pradilla, R.; Helgason, A. L. *J. Org. Chem.* **1994**, 59, 5514.

³¹ For related heteroenyne cycloadditions, see: Wills, M. S. B.; Danheiser, R. L. *J. Am. Chem. Soc.* **1998**, 120, 9378.

³² For intramolecular [4 + 2] cycloadditions of arynes with conjugated enynes and arenynes, see: Hayes, M. E.; Shinokubo, H.; Danheiser, R. L. *Org. Lett.* **2005**, 7, 3917.

³³ For a more detailed discussion of the background, scope, and mechanism of the enyne and related cycloadditions, see: (a) Helgason, A. E. Ph. D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, June 1994. (b) Gould, A. E. Ph. D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, June 1996. (c) Palucki, B. L. Ph. D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, June 1997. (d) Mayes, M. E. Ph. D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, June 2004.

³⁴ For reviews of related transition-metal-catalyzed enyne cycloadditions, see: (a) Rubin, M.; Sromek, A. W.; Gevorgyan, V. *Synlett* **2003**, 2265. (b) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, 100, 2901. (c) Gevorgyan, V.; Yamamoto, Y. *J. Organomet. Chem.* **1999**, 576, 232.

Table 1. Representative Intramolecular [4 + 2] Cycloadditions of Conjugated Enynes

entry	substrate	conditions ^a	product	yield ^b
		Δ		
1	57 (Z = H)	1 equiv PMP ^c , 250 °C, 24 h	66	26% ^d
2	58 (Z = CO ₂ Me)	1 equiv BHT, 180 °C, 15 h	67	85%
3	59 (Z = C≡CSiMe ₃)	3 equiv PMP, 180 °C, 3 h	68	80%
4	60	3 equiv BHT, 180 °C, 16 h	69	78%
5	60	2.5 equiv MsOH, 0 °C, 30 min ^e	69	87%
6	60	1.1 equiv AlCl ₃ , 0 °C, 30 min ^e	69	90%
		3 equiv BHT		
7	61 (R = H, Z = Ts)	180 °C, 4 h	70	60%
8	62 (R = CH ₃ , Z = Bn)	180 °C, 19 h	71	64%
		3 equiv BHT 150 °C, 21 h		
9	63		72	78%
		1) 1.5 equiv DMP 2) 3 equiv BHT, 80 °C, 3 h		
10	64		73	88% (2 steps)
		3 equiv BHT 120 °C, 2 h		
11	65		74	33%

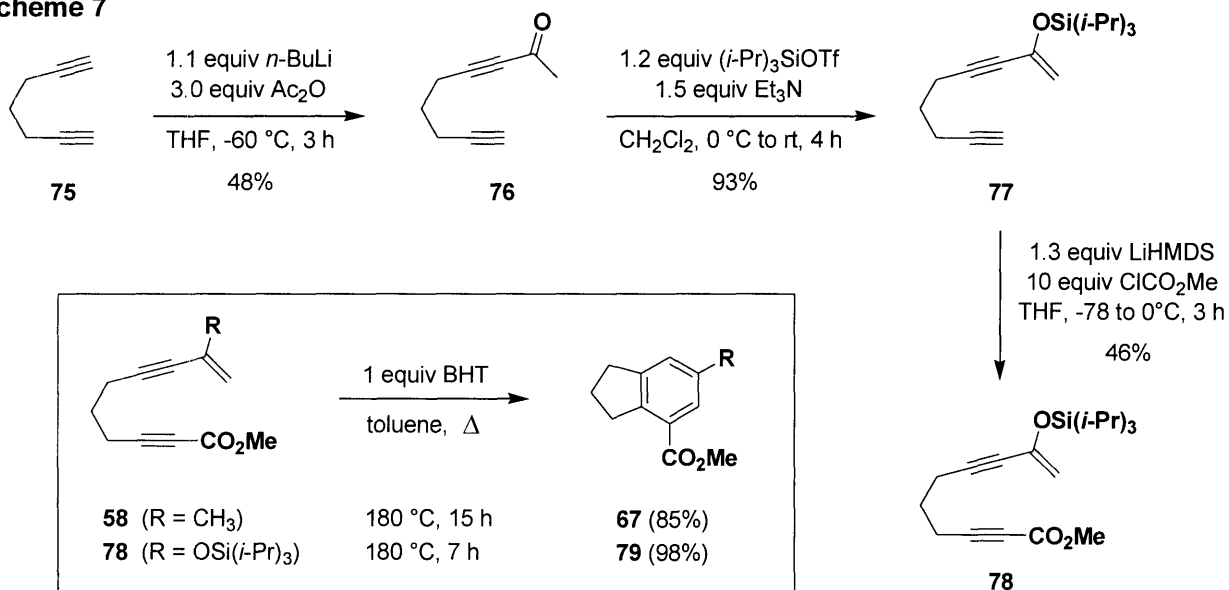
^a Reactions in degassed toluene (0.1 M) unless otherwise noted. ^b Isolated yields of products purified by column chromatography. ^c PMP is *p*-methoxyphenol. ^d Product obtained in 35% yield and 75% purity (by ¹H NMR analysis). ^e Reaction in CH₂Cl₂ (0.05 M).

Interestingly, the yields for thermal cycloadditions in Table 1 benefit from the presence of phenolic additives such as BHT or *p*-methoxyphenol (PMP). Although originally included to suppress the polymerization of these highly unsaturated substrates at elevated temperatures, we now believe these phenolic additives play a role in the isomerization of the cyclic allene intermediates to aromatic products (*vide infra*). These additives generally improve the reaction yields by 10–20% without affecting the rate of cycloaddition.

As expected, the rate and efficiency of cycloaddition both improve when the enynophile is activated by an electron-withdrawing group (Table 1, compare entries 1 and 2). The cycloadditions of conjugated enynes with diynes (entry 3) are noteworthy in that the enynophile is activated by another acetylenic unit, presumably through inductive effects. Both protic and Lewis acids promote the reaction at low temperatures and provide alternatives to thermal conditions (entries 4–6). Heteroatoms in the connecting tether allow for the synthesis of heterocycles and in some cases activate the substrate for cycloaddition (compare entries 1 and 8). Entropic constraints favor cycloaddition, and substrates with rigid benzene tethers holding the enyne and enynophile in close proximity undergo thermal cycloaddition at temperatures as low as 80 °C (entry 10). Finally, former group member Brenda Palucki was the first to explore the intramolecular [4 + 2] cycloaddition of a conjugated enyne and ynamide for the synthesis of carbazole **74** (entry 11). Although this reaction furnishes the carbazole in only modest yield, it provides important precedent for the synthesis of indolines and indoles via similar cycloadditions of enynes with ynamides.

As shown in Table 1, electron-withdrawing groups activate enynophiles for cycloaddition, and we were curious as to whether electron-donating groups on the enyne would similarly enhance the rate and efficiency of this reaction. The synthesis and cycloaddition of electron-rich enyne **78** are shown in Scheme 7. While the rate of cycloaddition increases with the electron-density of the enyne (compare the reactions of **58** and **78**), the rate enhancement is modest in comparison to the effects of enynophile activation with electron-withdrawing groups (*vide supra*). The efficiency of converting enyne to indan also increases with the strength of electron-donating groups on the 4 π component, as the thermolysis of **78** afforded **79** in near quantitative yield.

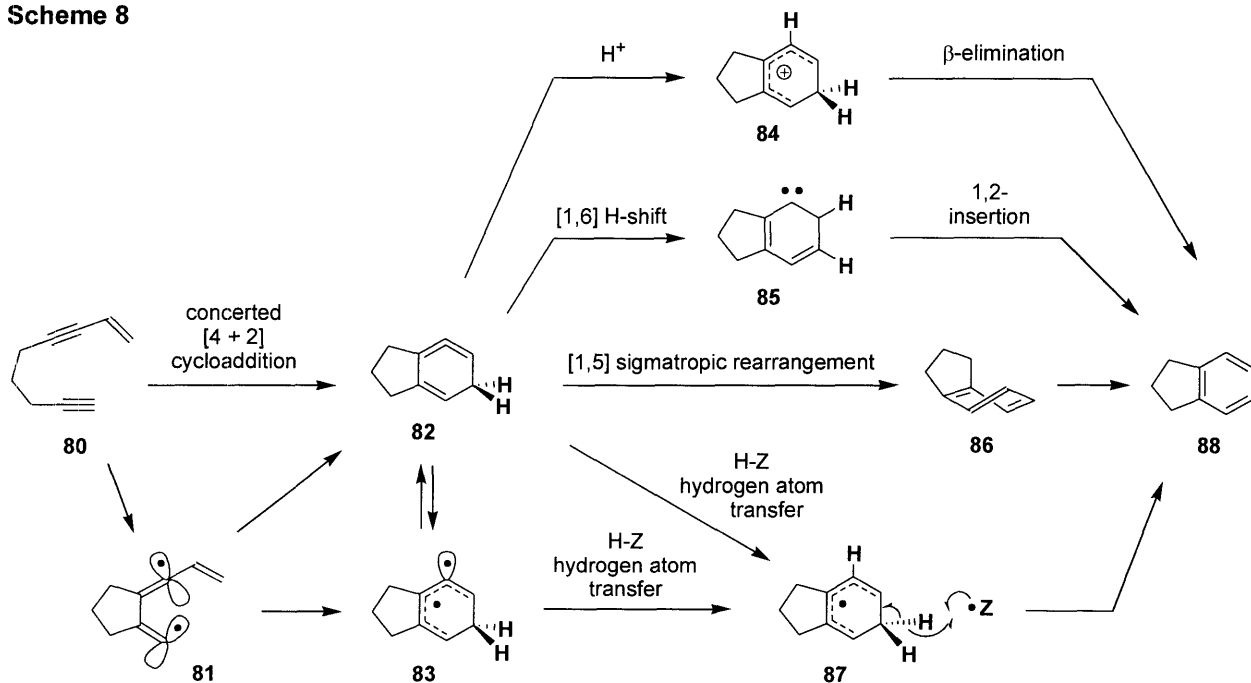
Scheme 7



Mechanism of [4 + 2] Cycloadditions of Conjugated Enynes

In addition to exploring the scope and utility of intramolecular enyne cycloadditions, our laboratory has also investigated the mechanism of these remarkable transformations. Several possible mechanistic pathways for the conversion of enyne **80** to indan **88** are outlined in

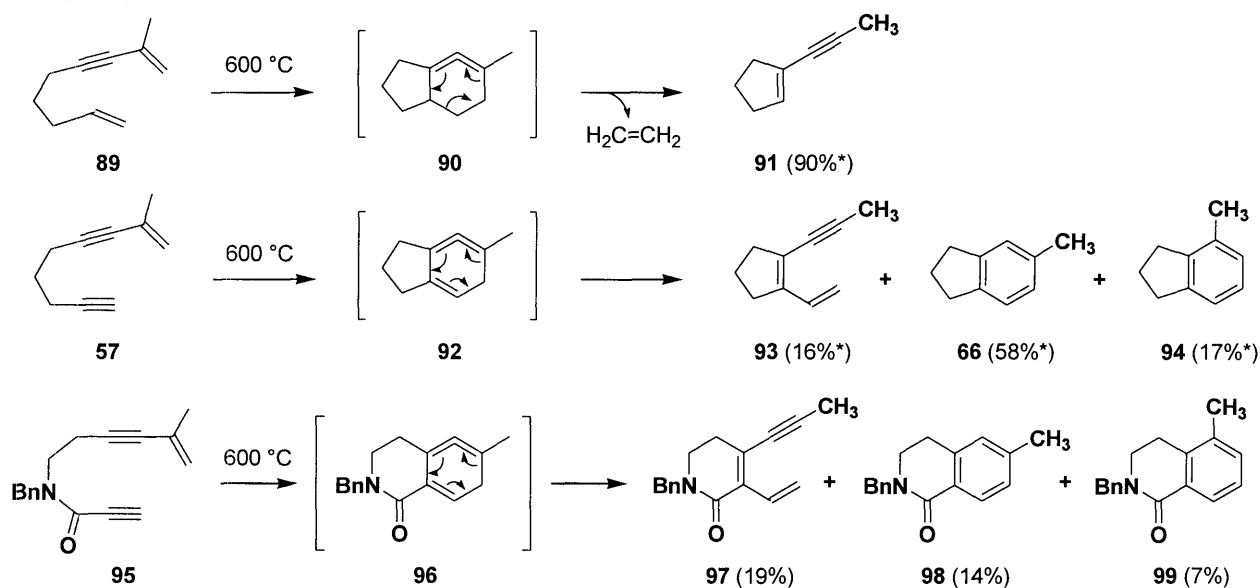
Scheme 8



Scheme 8. It has been postulated that the thermal cycloaddition of a conjugated enyne and alkyne produces a highly strained isoaromatic cyclic allene of type **82**. While six-membered cyclic allenes such as **82** have not been isolated, they are known and have been successfully trapped in [4 + 2] and [2 + 2] cycloadditions.³⁵

In 1996, Johnson reported evidence for the intermediacy of cyclic allenes in enyne cycloadditions with a series of flash vacuum pyrolysis experiments (Scheme 9).²⁰ The gas-phase thermolysis of enyne **89** generates **91** in high yield with the loss of ethylene, which is consistent with a [4 + 2] cycloreversion of possible allene intermediate **90**. Similar flash vacuum pyrolysis of enyne **57** furnishes small amounts of **93**, which is the 6 π electrocyclic ring opening product of possible intermediate **92**. Similar flash vacuum pyrolysis experiments were conducted in our laboratory by Brenda Palucki with enyne **95**.^{33c} The gas-phase thermolysis of **95** provided **97**, which is consistent with a 6 π electrocyclic ring opening of cyclic allene **96**.

Scheme 9

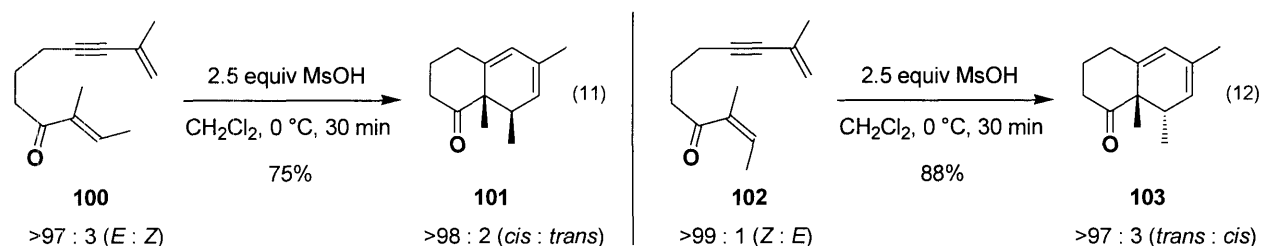


(* Yield based on recovered starting material with 50-80% conversion)

The cycloaddition of **80** may occur through a concerted or stepwise process (Scheme 8). A concerted mechanism forms two new σ bonds in a single step, whereas a stepwise process generates biradical **81** as an intermediate. Both pathways can lead to cyclic allene **82**, which

³⁵ For reviews, see: (a) Christl, M. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2003; pp 248–324. (b) Hopf, H. In *Classics in Hydrocarbon Chemistry*; Wiley-VCH: New York, 2000; pp 182–187.

might exist in equilibrium with biradical **83** depending on the stabilizing effects of substituents on the six-membered ring.³⁶ As previously discussed, electron-withdrawing groups on the enynophile activate enyne substrates for cycloaddition, which suggests that these reactions might be *concerted* processes governed by frontier molecular orbital interactions. Electron-withdrawing groups can also stabilize radical intermediates of type **81** in stepwise reactions; however, the ability of Lewis acids to accelerate enyne cycloadditions with electron-deficient alkynes further supports a concerted mechanism for these reactions. Studies from our laboratory concerning the stereospecificity of enyne cycloadditions with tethered alkenes also provide compelling evidence for a concerted mechanism. Visiting scientist Dr. Roberto Fernández de la Pradilla explored the reactions of *cis*- and *trans*-alkenes as enynophiles, and he observed that the geometry of the olefin is retained in the product (eq 11–12). These results are consistent with concerted cycloadditions that are suprafacial with respect to the enynophile. Furthermore, theoretical studies by Ananikov predict that both intramolecular and intermolecular [4 + 2] cycloadditions of conjugated enynes with alkynes are concerted processes, and that the initial formation of a cyclic allene intermediate is the rate determining step for the conversion of enyne substrates to aromatic products. Ab initio calculations suggest that related *arenynes*, however, may undergo cycloaddition in a stepwise fashion.³⁷



After the initial formation of cyclic allene **82**, there are several isomerization pathways that lead to the aromatic product (Scheme 8). One unimolecular mode of cyclic allene isomerization involves a [1,5] sigmatropic rearrangement which would provide the aromatic product through a transient *cis,cis,trans*-1,3,5-cyclohexatrienyl intermediate **86** similar to Möbius benzene.³⁸ An alternative unimolecular pathway involves a [1,6] sigmatropic

³⁶ Engels, B.; Schöneboom, J. C.; Münster, A. F.; Groetsch, S.; Christl, M. *J. Am. Chem. Soc.* **2002**, *124*, 287.

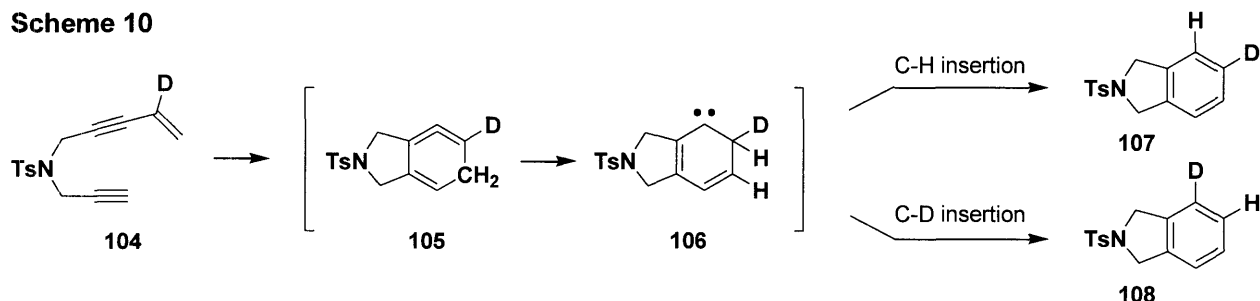
³⁷ Rodríguez, D.; Navarro, A.; Castedo, L.; Domínguez, D.; Saá, C. *Org. Lett.* **2000**, *2*, 1497.

³⁸ For studies of Möbius benzene, see: Johnson, R. P.; Daoust, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 7381 and references therein.

rearrangement to generate carbene **85** followed by 1,2-insertion into the adjacent carbon-hydrogen bond. Theoretical studies by Ananikov,²¹ Hopf,³⁹ and Saá⁴⁰ predict the activation energy for the formation of **86** via direct [1,5] sigmatropic rearrangement is higher than pathways leading to carbene **85**. In addition, the methyl migration observed in products **94** and **99** from flash vacuum pyrolysis experiments (Scheme 9) is consistent with carbene intermediates that insert into the adjacent carbon-carbon bonds.

While the unimolecular isomerization of cyclic allenes to aromatic products through carbene intermediates may occur in the gas phase, products such **94** and **99** have not been detected in solution-phase reactions. To evaluate the possibility of carbene intermediates in solution (or at temperatures below 600 °C), former group member Martin Hayes explored the cycloaddition of deutero enyne **104** in toluene at 180 °C.^{33d} If the isomerization of cyclic allene **105** proceeds via carbene **106**, then competitive 1,2-insertion into the carbon-deuterium bond would lead to **108** as a side product.⁴¹ The cycloaddition of deutero enyne **104**, however, led to **107** as the only regioisomer in the absence of phenolic additives which might intercept the cyclic allene through donation of a proton or hydrogen atom (vide infra). The absence of **108** suggests that the solution-phase isomerization of cyclic allene intermediates to aromatic products does not proceed via carbene intermediates such as **106** (or **85**, Scheme 8).

Scheme 10



Theoretical calculations predict that the most energetically favorable pathway for unimolecular isomerization involves carbenes of type **85** (or **106**).^{21,39,40} Since evidence suggests these carbenes are not generated from cyclic allenes in solution-phase reactions, then under these

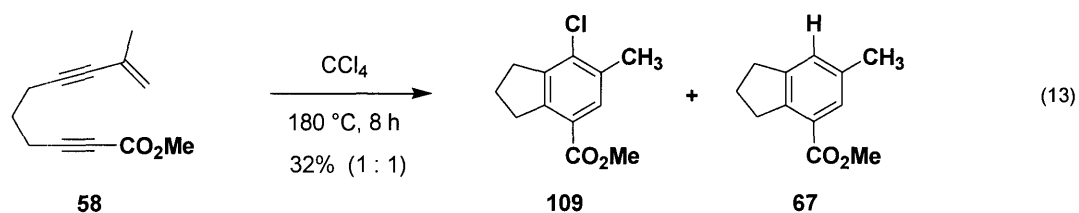
³⁹ Prall, M.; Krüger, A.; Schreiner, P. R.; Hopf, H. *Chem. Eur. J.* **2001**, 7, 4386.

⁴⁰ Rodríguez, D.; Navarro-Vázquez, A.; Castedo, L.; Domínguez, D.; Saá, C. *J. Org. Chem.* **2003**, 68, 1938.

⁴¹ Nickon measured the migratory aptitude of hydrogen versus deuterium for exo- and endocyclic hydrogen atoms adjacent to a carbene on a constrained bicyclic system and found that hydrogen is 1.3 times more likely to migrate than deuterium. See: Nickon, A.; Huang, F.-c.; Weglein, R.; Matsuo, K.; Yagi, H. *J. Am. Chem. Soc.* **1974**, 96, 5264.

conditions it seems likely that isomerization must occur through *bimolecular* processes. As previously discussed, we believe phenols facilitate the isomerization of these isoaromatic intermediates via transfer of a proton or hydrogen atom to the cyclic allene, and additives such as BHT generally improve the yields of aromatic products by 10–20% without affecting the rate of cycloaddition. The intermolecular transfer of a proton to the cyclic allene would lead to a pentadienyl cation of type **84** and subsequent β -elimination would furnish the aromatic product. Similarly, the intermolecular donation of a hydrogen atom to the cyclic allene would form a pentadienyl radical of type **87** which becomes the aromatic product after hydrogen atom abstraction.

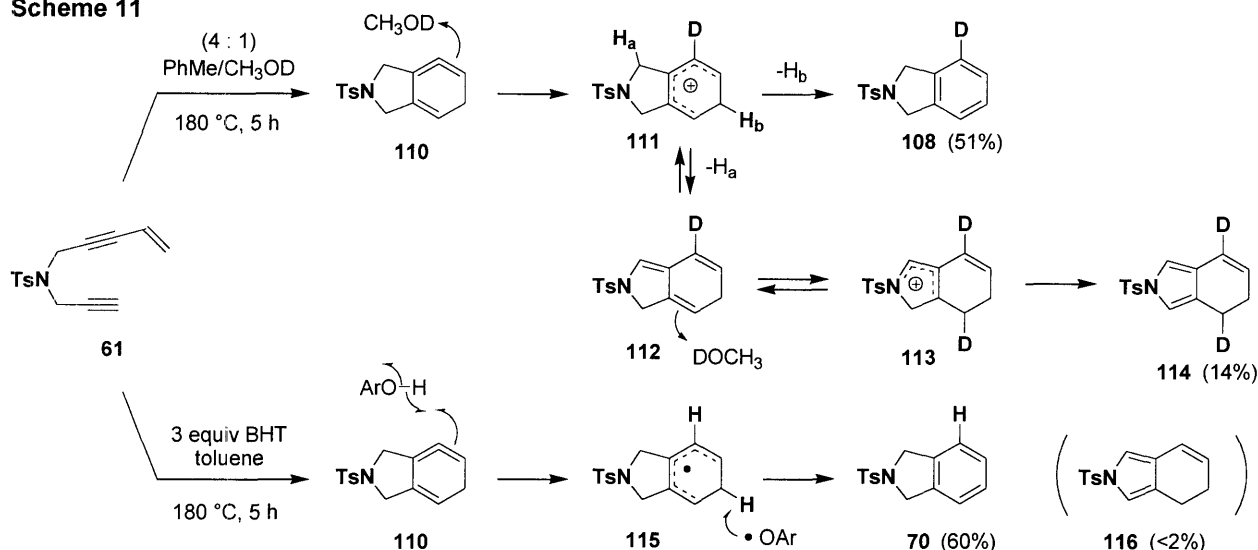
Experiments conducted in our laboratory provide evidence for the isomerization of cyclic allene intermediates via bimolecular proton or hydrogen (or halogen) atom abstraction processes. As shown below, cycloadditions conducted in carbon tetrachloride by Alexandra Gould furnish aryl chlorides after donation of a chlorine radical to the central carbon of the allene.^{30,42} In addition, Martin Hayes found compelling evidence that alcoholic solvents transfer a proton to the



cyclic allene intermediates.^{33d} The cycloaddition of **61** in d_1 -methanol generates a 79:21 mixture of deuterated products **108** and **114** in a combined 65% yield (Scheme 11). Pyrrole **114** is derived from **110** after protonation of the allene, β -elimination of the H_a proton, and acid-catalyzed olefin migration. Phenols are generally more acidic than alcohols, and we might expect that similar protonation of **110** by BHT would lead to a mixture of **70** and pyrrole **116**. Thermolysis of **61** in toluene in the presence of BHT, however, leads to **70** in 60% yield and only trace amounts of pyrrole **116** are detected. While the preference for loss of H_a versus H_b from pentadienyl cations such as **111** can vary depending on the reaction conditions (i.e., deprotonation by methoxide versus phenoxide), we also considered the possibility that BHT facilitates the isomerization of cyclic allenes as a hydrogen atom transfer agent. Further

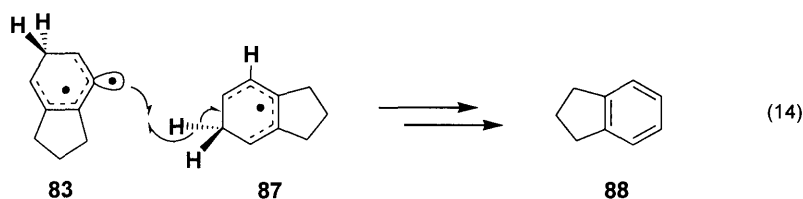
⁴² Theoretical studies support the donation of a chlorine radical to the cyclic allene rather than a chlorine cation. See ref 40.

Scheme 11



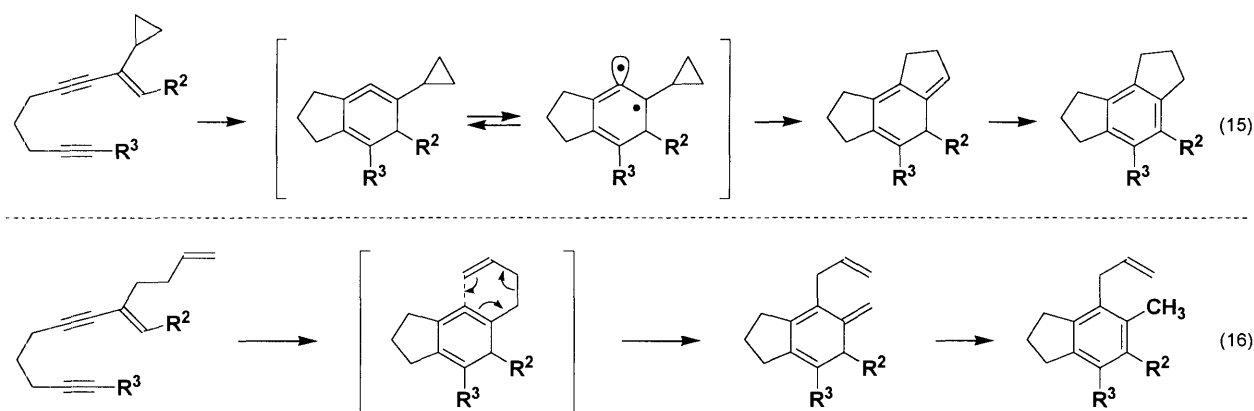
evidence for the participation of BHT as a hydrogen atom donor to the cyclic allene will be presented later in this thesis.

In the absence of obvious proton or hydrogen atom sources such as alcohols or phenols, the isomerization of cyclic allenes in solution-phase reactions may proceed via bimolecular radical chain reaction sequences as shown below. These reaction pathways would require a sufficiently long lifetime for highly reactive intermediates, and appear unlikely at the low concentrations (typically 0.05–0.1 M) employed for enyne cycloadditions. More likely proton or hydrogen atom sources include reaction solvents such as toluene or THF, as well as the highly unsaturated cycloaddition substrates and products.

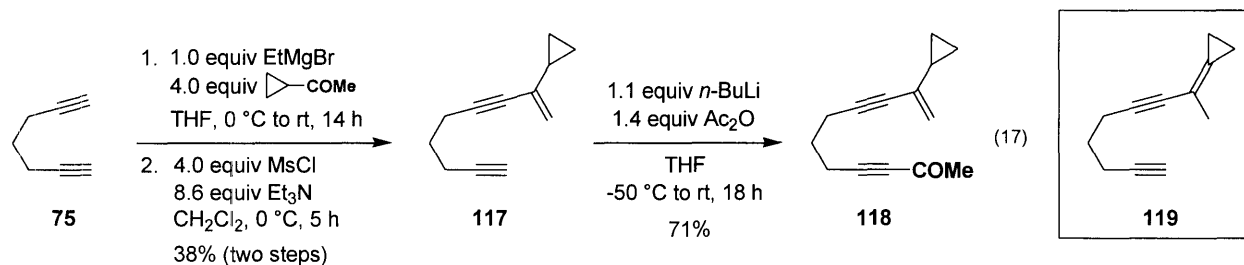


The donation of a proton or hydrogen atom to the central carbon of the cyclic allene does not allow for substitution at this position in the aromatic product. Previous attempts to intercept the allene with a chlorine atom have led only to partial chlorine incorporation into the aromatic products (eq 13). We investigated two strategies for the interception of the isoaromatic intermediate that would introduce a new carbon-carbon σ bond to the central atom of the allene and provide substitution at a previously elusive position. As shown below, the trapping of

isoaromatic or biradical intermediates via vinylcyclopropane or Cope rearrangements would add a carbon substituent to the central carbon of the allene and provide further evidence for the intermediacy of cyclic allenes.



The preparation of substrate **118** for tandem enyne cycloaddition-vinylcyclopropane rearrangement is shown below. Deprotonation of **75** and Grignard addition to cyclopropyl methyl ketone generated a tertiary alcohol, and elimination of the mesylate derivative afforded cyclopropyl enyne **117**. We did not detect **119** as an alternative elimination product. Activation of the enynophile of **117** via acylation then provided substrate **118** for cycloaddition.

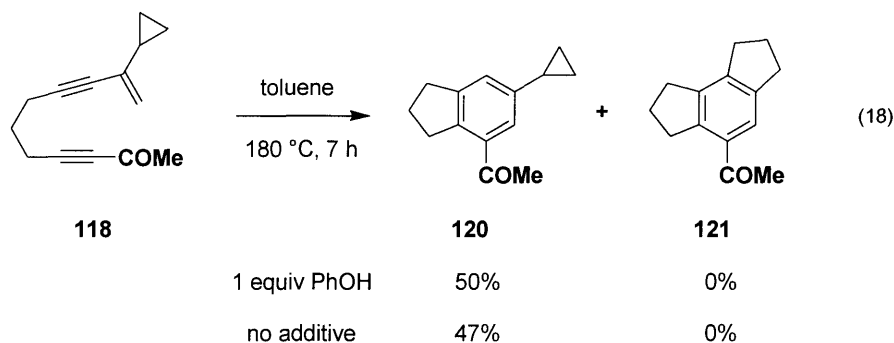


Vinylcyclopropane rearrangements⁴³ typically occur at very high temperatures in the range of 500–600 °C unless the system is substituted with an anion-accelerating group.⁴⁴ We speculated, however, that the strain of the vinylcyclopropane system embedded within the cyclic allene might facilitate rearrangement at lower temperatures. We also believed that the possible

⁴³ For a review of vinylcyclopropane rearrangements, see: (a) Hudlicky, T.; Reed, J. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Oxford: Pergamon, 1991; Vol. 5, pp 899–970. (b) Hudlicky, T.; Kutchan, T. M.; Naqvi, S. M. *Org. React.* **1985**, *33*, 247.

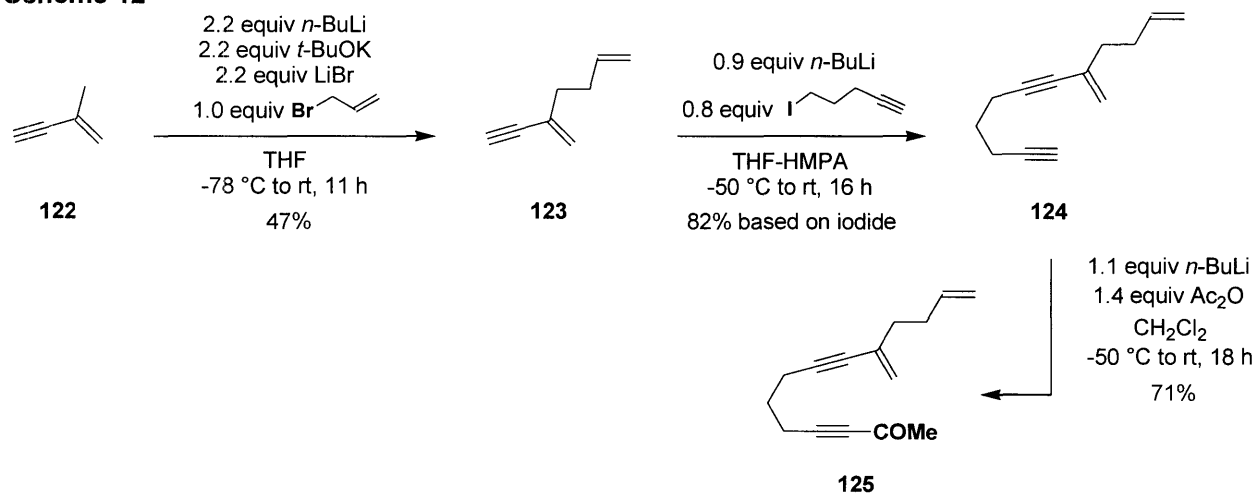
⁴⁴ For our previous investigations of oxyanion-accelerated vinylcyclopropane rearrangements, see: (a) Danheiser, R. L.; Martinez-Davila, C.; Morin, Jr., J. M. *J. Org. Chem.* **1980**, *45*, 1340. (b) Danheiser, R. L.; Martinez-Davila, C.; Auchus, R. J.; Kadonaga, J. T. *J. Am. Chem. Soc.* **1981**, *103*, 2443. (c) Danheiser, R. L.; Bronson, J. J.; Okano, K. *J. Am. Chem. Soc.* **1985**, *107*, 4579.

biradical intermediate shown in eq 15 might trigger the fragmentation of the cyclopropane ring. Thermolysis of **118** at 180 °C, however, failed to induce a tandem enyne cycloaddition-vinyl cyclopropane rearrangement that would provide **121**, even in the absence of phenolic additives which might intercept the cyclic allene. These results suggest that the rate of isomerization of the cyclic allene (and possible biradical intermediate) to aromatic products is faster than the vinylcyclopropane rearrangement at 180 °C.



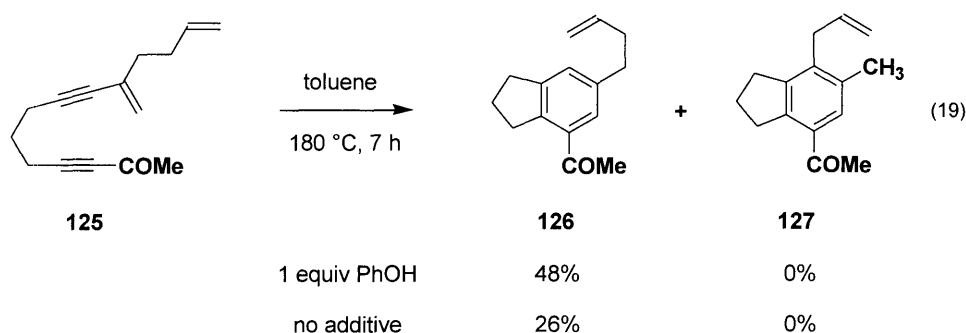
Scheme 12 outlines the synthesis of the substrate **125** required for our study of the tandem enyne cycloaddition-Cope rearrangement. Double metalation of isopropenylacetylene (**122**) with the Lochmann-Schlosser reagent *n*-BuLi/*t*-BuOK and conversion to the dilithium species with LiBr provided **123** after alkylation with allyl bromide.⁴⁵ Deprotonation of enyne **123** and alkylation with 1-iodo-4-pentyne installed the 2 π component, and acylation provided substrate **125** for cycloaddition.

Scheme 12



⁴⁵ Klusener, P. A. A.; Kulik, W.; Brandsma, L. *J. Org. Chem.* **1987**, 52, 5261.

Thermal Cope rearrangements generally occur at temperatures ranging from 150–250 °C, although these reactions are known to proceed at lower temperatures when the 1,5-dienes are cyclic and ring strain is relieved.⁴⁶ As proposed in eq 16, we investigated whether the strained cyclic allene intermediate of enyne cycloaddition would undergo a [3,3] sigmatropic rearrangement with a tethered alkene. Thermolysis of **125** at 180 °C, however, generated **126** as the exclusive indan product and did not induce a tandem enyne cycloaddition-Cope rearrangement to afford **127**. It appears that under these conditions, the Cope rearrangement cannot compete with isomerization pathways that convert the cyclic allene intermediate to **126**.



Microwave-Assisted Cycloadditions of Conjugated Enynes

We considered the possibility that the cycloaddition of **125** at higher temperatures might promote the intramolecular Cope rearrangement of a cyclic allene intermediate over bimolecular isomerization pathways. To test our hypothesis, we turned our attention to enyne cycloadditions promoted by microwave irradiation, which is an effective method for heating substrates at temperatures beyond the capability of conventional oil baths.⁴⁷ It is well-documented that the rate and efficiency of cycloadditions often increase when classical heating is replaced with microwave irradiation.⁴⁸ Yields of cycloadducts improve when reactions are promoted with microwaves at higher temperatures for shorter durations of time, which minimizes the exposure of potentially sensitive reagents and products to elevated thermal conditions.

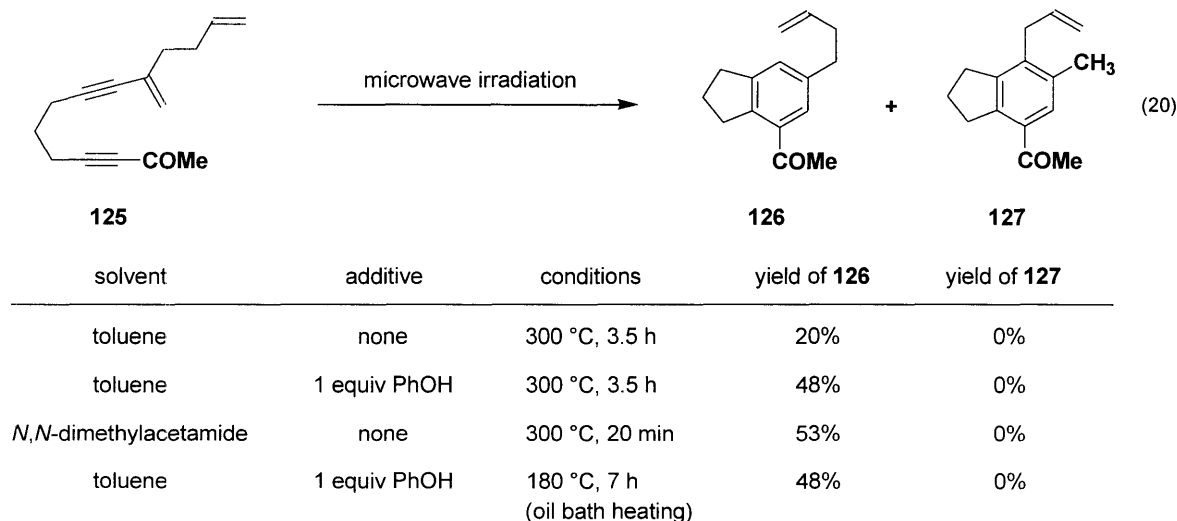
⁴⁶ For reviews of the Cope rearrangement, see: (a) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205. (b) Rhoads, S. J.; Raulins, N. R. *Org. React.* **1975**, *22*, 1.

⁴⁷ For a review of the use of microwaves in organic synthesis, see: de la Hoz, A.; Díaz-Ortiz, Á.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164 and references therein.

⁴⁸ For a review of microwave-assisted cycloadditions, see: de la Hoz, A.; Díaz-Ortiz, Á.; Moreno, A.; Langa, F. *Eur. J. Org. Chem.* **2000**, *22*, 3659.

Microwave heating occurs when molecules (i.e., reagents, products, and solvent) absorb microwaves and transform this energy into heat.⁴⁷ The efficiency of microwave heating depends on the dielectric constant (which is related to the ability to absorb microwaves) and the dielectric loss factor (ability to transform microwave energy into heat) of a particular compound. Whereas conventional oil baths heat the surface of a reaction vessel, microwave energy is delivered directly to the molecules of the reaction mixture, heating the entire volume more uniformly. Local “hot spots” may still occur, and these concentrated points of thermal energy are significantly hotter than the mean temperature of the reaction media. These inhomogeneous zones of increased temperature often accelerate the reactions of nearby compounds and partially account for rate enhancements often observed via microwave irradiation.⁴⁷

As shown below, we explored the cycloaddition of **125** via microwave irradiation at 300 °C in both toluene and *N,N*-dimethylacetamide (DMA). Experiments were conducted in a Discovery System Microwave (CEM Corporation, 300 Watt capability) and the internal temperature was measured by infrared detection. Unfortunately, once again we isolated **126** as the only indan product under various conditions and could not detect any of the Cope rearrangement product **127**. We observed that reactions of **125** in toluene require 3.5 h to proceed to completion, whereas the cycloaddition in DMA is complete after 20 min. This rate enhancement may result from the higher concentration of rate-accelerating “hot spots”, which appear more frequently in polar media such as DMA that can better absorb microwaves and convert the energy to heat.⁴⁹



⁴⁹ Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev.* **1998**, 27, 213.

Summary

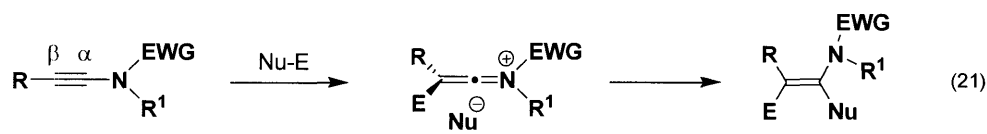
As discussed throughout this chapter, our laboratory has explored the scope and mechanism of intramolecular [4 + 2] cycloadditions of conjugated enynes for over a decade. The application of this strategy to the synthesis of highly substituted indolines and indoles via cycloaddition of ynamides and conjugated enynes will be the topic of discussion in subsequent chapters of Part I of this thesis.

Chapter 3

Background: Strategies for the Synthesis of Ynamides

In recent years, ynamides have emerged as powerful building blocks for organic synthesis.⁵⁰ In comparison to ynamines, ynamides are more easily stored and handled and tolerate a variety of conditions destructive to typical ynamines. The relative stability of ynamides stems from an electron-withdrawing group on the nitrogen which diminishes the ability of the heteroatom to donate electron density into the adjacent π system. As a result, these alkynes are less sensitive toward hydrolysis and more resistant to polymerization at high temperatures.

The nitrogen atom of ynamides imposes an electronic bias on the adjacent alkyne and influences the reactivity of these acetylenes. Ynamides are basic and nucleophilic at the β -alkynyl position and additions across the π system proceed with the regioselectivity shown below. For example, acid-catalyzed additions of allylic and propargylic alcohols to ynamides



occur via protonation at the β -alkynyl carbon and generate ketenimine acetals for subsequent Ficiini-Claisen⁵¹ or Saucy-Marbet⁵² rearrangements. Electrophilic additions of aldehydes to ynamides in the presence of Lewis acids also occur at the β -position.⁵³ Furthermore, this mode

⁵⁰ For reviews, see: (a) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, 1379. (b) Zifcsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, 57, 7575. (c) Himbert, G. In *Methoden der Organischen Chemie (Houben-Weyl)*; Kropf, H.; Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1993; Vol. E15, Part 3, pp 3267–3443.

⁵¹ Mulder, J. A.; Hsung, R. P.; Frederick, M. O.; Tracey, M. R.; Zifcsak, C. A. *Org. Lett.* **2002**, 4, 1383.

⁵² Frederick, M. O.; Hsung, R. P.; Lambeth, R. H.; Mulder, J. A.; Tracey, M. R. *Org. Lett.* **2003**, 5, 2663.

⁵³ (a) Hsung, R. P.; Zifcsak, C. A.; Wei, L.-L.; Douglas, C. J.; Xiong, H.; Mulder, J. A. *Org. Lett.* **1999**, 1, 1237. (b) Tanaka, R.; Hirano, S.; Urabe, H.; Sato, F. *Org. Lett.* **2003**, 5, 67. (c) Hirano, S.; Tanaka, R.; Urabe, H.; Sato, F. *Org. Lett.* **2004**, 6, 727.

of reactivity allows ynamides to serve as precursors to α -halo,⁵⁴ α -stannyl,⁵⁵ and β -boro enamides⁵⁶ which participate in subsequent coupling reactions.

Ynamides are also versatile participants in a variety of ring-forming processes. Several groups have utilized these compounds in Pauson-Khand reactions to access cyclopentenones with amino substituents.⁵⁷ Ynamides participate in cycloadditions^{16,29e} and related cyclotrimerizations⁵⁸ for the synthesis of indolines and carbazoles, while other nitrogen heterocycles are available from the reaction of these amido alkynes in Pictet-Spengler-type cyclizations,⁵⁹ Heck cyclizations,⁶⁰ aza-Bergman rearrangements,⁶¹ and radical cyclization cascades.⁶² In addition, recent studies on enyne metatheses⁶³ and cycloisomerizations⁶⁴ have extended the scope of these important ring-forming reactions to include ynamide substrates.

Isomerization and Elimination Strategies for the Synthesis of Ynamides

When we first became interested in exploring the application of intramolecular [4 + 2] enyne cycloadditions as a route to indolines and indoles, there were several methods available for the synthesis of the ynamide cycloaddition substrates we planned to study. One of the oldest strategies for the synthesis of ynamides involves the base-catalyzed isomerization of propargyl amides. Zaugg discovered this method serendipitously upon treating phenothiazine with sodium

⁵⁴ Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P.; Coverdale, H.; Frederick, M. O.; Shen, L.; Zifcick, C. A. *Org. Lett.* **2003**, *5*, 1547.

⁵⁵ (a) Minière, S.; Cintrat, J.-C. *Synthesis* **2001**, 705. (b) Timbart, L.; Cintrat, J.-C. *Chem. Eur. J.* **2002**, *8*, 1637. (c) Naud, S.; Cintrat, J.-C. *Synlett* **2003**, 1391.

⁵⁶ Witulski, B.; Buschmann, N.; Bergsträsser, U. *Tetrahedron* **2000**, *56*, 8473.

⁵⁷ (a) Witulski, B.; Stengel, T. *Angew. Chem. Int. Ed.* **1998**, *37*, 489. (b) Rainier, J. D.; Imbriglio, J. E. *Org. Lett.* **1999**, *1*, 2037. (c) Witulski, B.; Gössmann, M. *Chem. Commun.* **1999**, 1879. (d) Witulski, B.; Gössmann, M. *Synlett* **2000**, 1793. (e) Rainier, J. D.; Imbriglio, J. E. *J. Org. Chem.* **2000**, *65*, 7272. (f) Shen, L.; Hsung, R. P. *Tetrahedron Lett.* **2003**, *44*, 9353.

⁵⁸ (a) Witulski, B.; Stengel, T. *Angew. Chem. Int. Ed.* **1999**, *38*, 2426. (b) Witulski, B.; Stengel, T.; Fernández-Hernández, J. M. *Chem. Commun.* **2000**, 1965. (c) Witulski, B.; Alayrac, C. *Angew. Chem. Int. Ed.* **2001**, *41*, 3281.

⁵⁹ Zhang, Y.; Hsung, R. P.; Zhang, X.; Huang, J.; Slafer, B. W.; Davis, A. *Org. Lett.* **2005**, *7*, 1047.

⁶⁰ (a) Witulski, B.; Alayrac, C.; Tevzadze-Saeftel, L. *Angew. Chem. Int. Ed.* **2003**, *42*, 4257. (b) Couty, S.; Liégault, B.; Meyer, C.; Cossy, J. *Org. Lett.* **2004**, *6*, 2511.

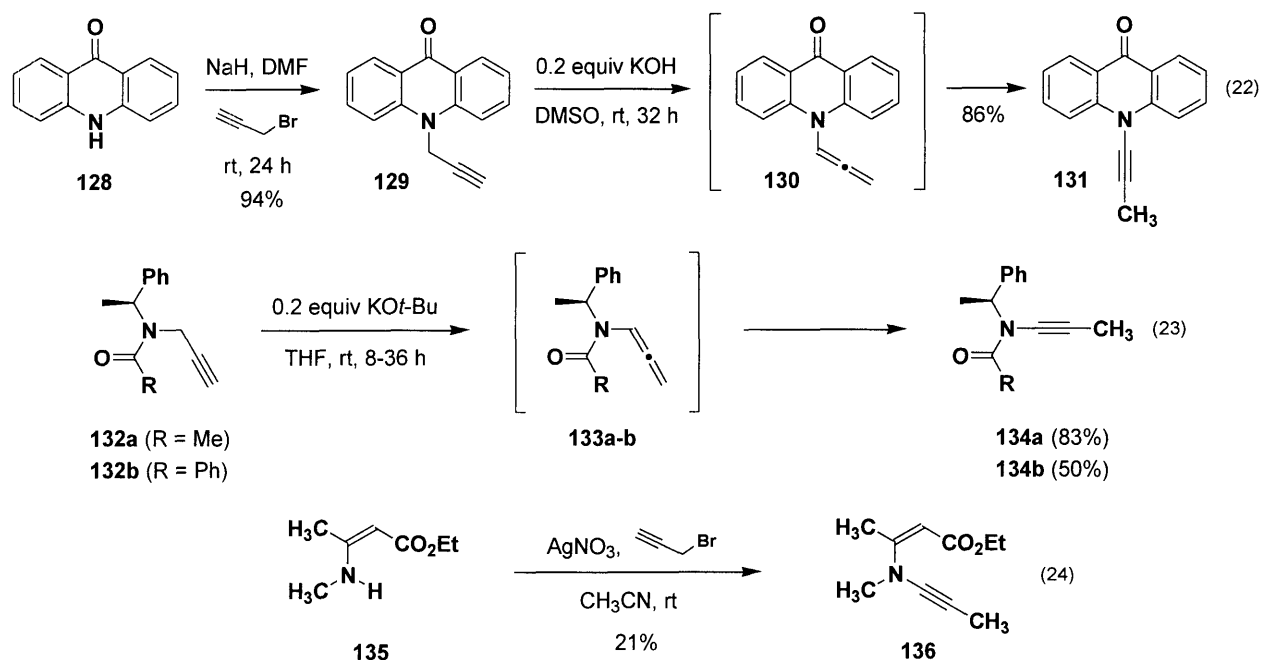
⁶¹ (a) David, W. M.; Kerwin, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 1464. (b) Nadipuram, A. K.; David, W. M.; Kumar, D.; Kerwin, S. M. *Org. Lett.* **2002**, *4*, 4543. (c) Feng, L.; Kumar, D.; Kerwin, S. M. *J. Org. Chem.* **2003**, *68*, 2234. (d) Klein, M.; König, B. *Tetrahedron* **2004**, *60*, 1087.

⁶² Marion, F.; Courillon, C.; Malacria, M. *Org. Lett.* **2003**, *5*, 5095.

⁶³ (a) Saito, N.; Sato, Y.; Mori, M. *Org. Lett.* **2002**, *4*, 803. (b) Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar, C.; Mulder, J. A.; Grebe, T. P. *Org. Lett.* **2002**, *4*, 2417. (c) Rosillo, M.; Domínguez, G.; Casarrubios, L.; Amador, U.; Pérez-Castells, J. *J. Org. Chem.* **2004**, *69*, 2084.

⁶⁴ Marion, F.; Coulomb, J.; Courillon, C.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 1509.

amide and propargyl bromide.⁶⁵ In subsequent years, Katritzky,⁶⁶ Majumdar,⁶⁷ Hsung,^{53a,68} and Gravestock⁶⁹ developed isomerization conditions for the formation of ynamides in which the nitrogen atom is deactivated through conjugation to an electron-withdrawing group. As shown below, Hsung reported that propargyl amide **129** could be converted to the allenamide **130** by shortening the reaction time for isomerization.⁶⁸ The base-catalyzed isomerization of propargyl amides generally stops at the allenamide when the electron-withdrawing group is directly attached to the nitrogen atom; however, Hsung was able to apply this strategy successfully to the synthesis of ynamides **134a** and **134b**.^{63b} Gravestock later reported a tandem alkylation-isomerization protocol for the synthesis of ynamides such as **136** in a single pot (albeit in low yields).⁶⁹



Another important strategy for the synthesis of ynamides involves the elimination of halo enamide precursors. There are several methods available for the preparation of requisite halogenated enamides. For example, the addition of metalated amides to tetrachloroethylene affords trichloro enamides of type **138**, as Zemlicka demonstrated with the preparation of various

⁶⁵ Zaugg, H. R.; Swett, L. R.; Stone, G. R. *J. Org. Chem.* **1958**, *23*, 1389.

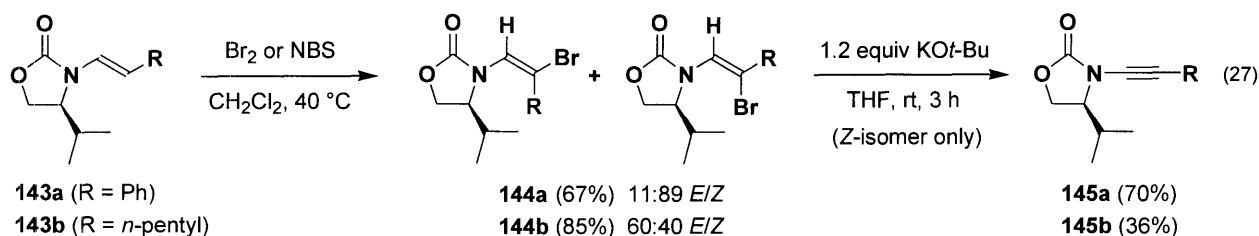
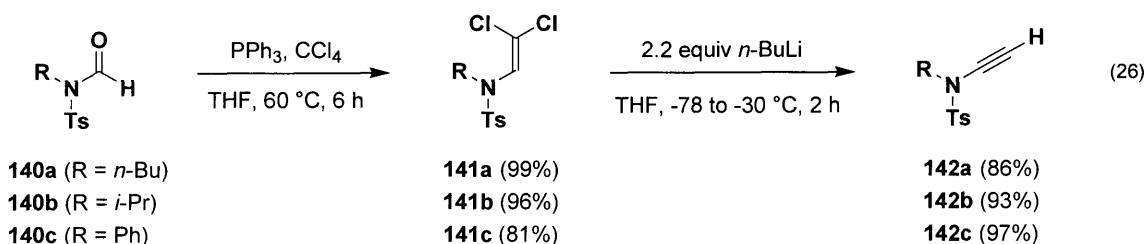
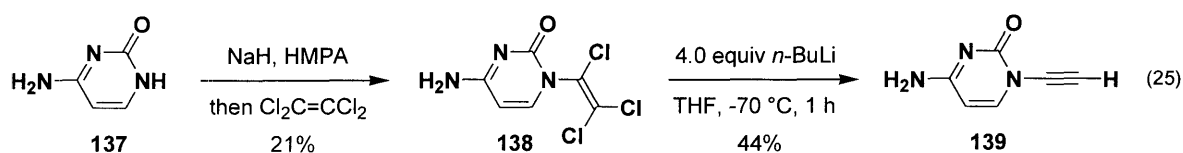
⁶⁶ Katritzky, A. R.; Ramer, W. H. *J. Org. Chem.* **1985**, *50*, 852.

⁶⁷ Majumdar, K. C.; Ghosh, S. K.; *Synth. Commun.* **1994**, *24*, 217.

⁶⁸ Wei, L.-L.; Mulder, J. A.; Xiong, H.; Zifcsak, C. A.; Douglas, C. J.; Hsung, R. P. *Tetrahedron* **2001**, *57*, 459.

⁶⁹ Gravestock, D.; Dovey, M. C. *Synthesis* **2003**, 523.

ynamides derived from pyrimidine derivatives (eq 25).⁷⁰ Elimination of **138** via metal-halogen exchange affords **139**. Brückner^{71a} and Hoffmann^{71b} generated *N*-dichlorovinyl tosylamides from *N*-formyl tosylamides using the protocol developed by Corey and Fuchs for the analogous conversion of aldehydes to *gem*-dihalo alkenes (eq 26).^{72,73} Hsung developed a third method for the preparation of halo enamides via bromination of enamides generated from the acid-catalyzed condensation of oxazolidinones and aldehydes.⁶⁸ The halogenation of **143a** and **143b**, however, provides a mixture of (*E*)- and (*Z*)-bromo enamides, and while the (*Z*)-isomers are converted to ynamides under basic conditions, the (*E*)-isomers do not undergo elimination (eq 27).



⁷⁰ Joshi, R. V.; Xu, Z.-Q.; Ksebati, M. B.; Kessel, D.; Corbett, T. H.; Drach, J. C.; Zemlicka, J. *J. Chem. Soc., Perkin Trans. I* **1994**, 1089.

⁷¹ (a) Brückner, D. *Synlett* **2000**, 1402. (b) Hoffmann, R. W.; Brückner, D. *New J. Chem.* **2001**, 25, 369.

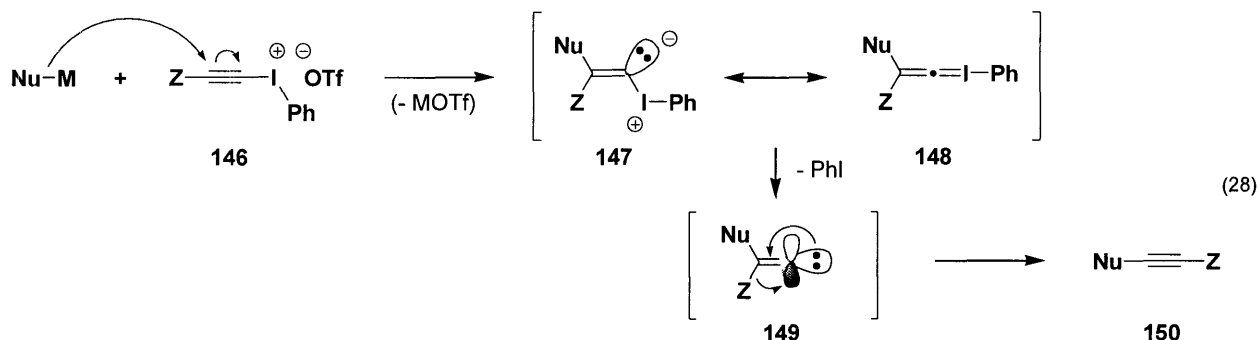
⁷² Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 13, 3769.

⁷³ For an application of Brückner and Hoffmann's method, see: Rodríguez, D.; Castedo, L.; Saá, C. *Synlett* **2004**, 783.

Synthesis of Ynamides via Alkynyl(phenyl)iodonium Salts

The addition of metalated amides to alkynyl(phenyl)iodonium salts such as **146** is another powerful strategy for the synthesis of ynamides.⁷⁴ These electrophilic iodonium reagents deliver alkynyl groups to a limited repertoire of soft nucleophiles. For example, alkynyl(phenyl)iodonium salts effect the alkynylation of 1,3-dicarbonyl carbanions⁷⁵ and organocopper reagents.⁷⁶ The addition of oxyanions such as metalated carboxylates, phosphates, and sulfonates to alkynyl(phenyl)iodonium salts provides access to alkynyl carboxylate, phosphate, and sulfonate esters.⁷⁷ The iodonium salts also react with certain sulfur nucleophiles to generate alkynyl thiocyanates⁷⁸ and thiotosylates.⁷⁹ Furthermore, other nucleophiles such as triphenylphosphine,⁸⁰ triphenylarsine,⁸¹ and diphenyl sulfide, selenide, and telluride⁸² undergo alkynylation via addition to these iodonium reagents.

Evidence suggests that these alkynylations proceed via rearrangements of alkylidenecarbene intermediates.^{74c,83} Addition of the nucleophile to the alkynyl(phenyl)iodonium species results in ylide **147/148** and the subsequent loss of



⁷⁴ For reviews of the synthesis and chemistry of alkynyl(phenyl)iodonium salts, see: (a) Stang, P. J. In *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, 1995; pp 67–98. (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (c) Zhdankin, V. V.; Stang, P. J. *Tetrahedron* **1998**, *54*, 10927. (d) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123. (e) Stang, P. J. *Angew. Chem. Int. Ed.* **1992**, *31*, 274.

⁷⁵ (a) Beringer, F. M.; Galton, S. A. *J. Org. Chem.* **1965**, *30*, 1930. (b) Ochiai, M.; Ito, T.; Takaoka, Y.; Masaki, Y.; Kunishima, M.; Tani, S.; Nagao, Y. *Chem. Commun.* **1990**, 118. (c) Bachi, M. D.; Bar-Ner, N.; Crittall, C. M.; Stang, P. J.; Williamson, B. L. *J. Org. Chem.* **1991**, *56*, 3912.

⁷⁶ For examples, see: (a) Kitamura, T.; Tanaka, T.; Taniguchi, H.; Stang, P. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2892. (b) Kitamura, T.; Lee, C. H.; Taniguchi, H.; Matsumoto, M.; Sano, Y. *J. Org. Chem.* **1994**, *59*, 8053.

⁷⁷ Stang, P. J. *Acc. Chem. Res.* **1991**, *24*, 304.

⁷⁸ Fischer, D. R.; Williamson, B. L.; Stang, P. J. *Synlett* **1992**, 535.

⁷⁹ Williamson, B. L.; Murch, P.; Fischer, D. R.; Stang, P. J. *Synlett* **1993**, 858.

⁸⁰ Stang, P. J.; Crittall, C. M. *J. Org. Chem.* **1992**, *57*, 4305.

⁸¹ Nagaoka, T.; Sueda, T.; Ochiai, M. *Tetrahedron Lett.* **1995**, *36*, 261.

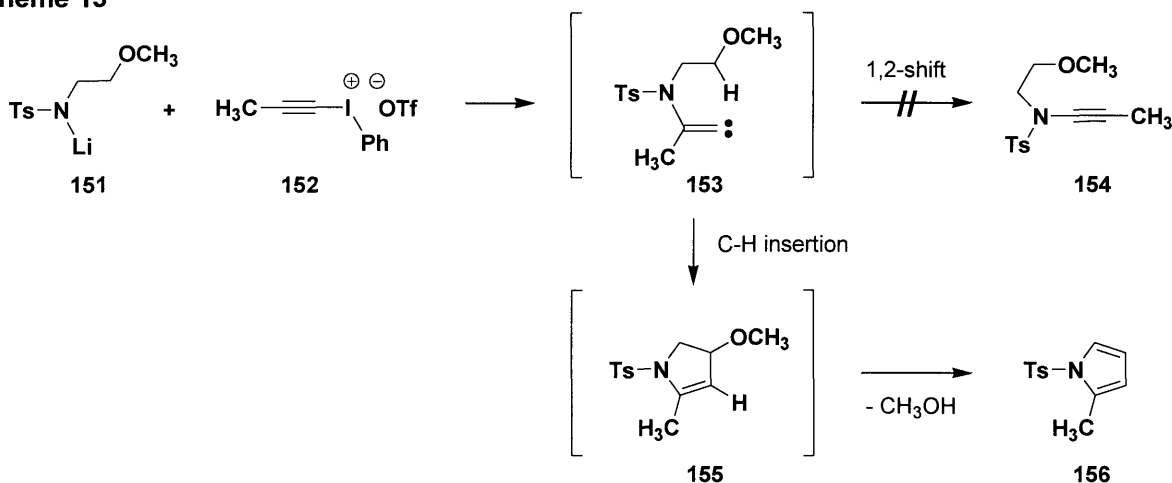
⁸² Ochiai, M.; Nagaoka, T.; Sueda, T.; Yan, J.; Chen, D.-W.; Miyamoto, K. *Org. Biomol. Chem.* **2003**, *1*, 1517.

⁸³ Kitamura, T.; Stang, P. J. *Tetrahedron Lett.* **1988**, *29*, 1887.

iodobenzene generates alkylidenecarbene **149**.⁸⁴ Rearrangement of **149** via 1,2-shift of the Z group then furnishes the alkynylation product.

While alkynyl(phenyl)iodonium salts are useful reagents for organic synthesis, there are several limitations regarding the use of these compounds in alkynylation reactions. For instance, these electrophiles are only compatible with soft nucleophiles such as those listed in the opening paragraph of this section. Harder nucleophiles such as organolithium compounds directly attack the iodine and decompose the onium salt through non-alkynylation pathways.⁸⁵ Furthermore, after suitably soft nucleophiles react with **146** via addition as shown in eq 28, the requisite 1,2-shift of alkylidenecarbene **149** only is a facile process when Z is a hydrogen atom or trialkylsilyl or aryl group.⁸⁶ The rearrangement is sluggish when Z is an alkyl group, and alkylidenecarbene intermediates can often then be intercepted by intramolecular carbon-hydrogen bond insertions.⁸⁷ For example, the slow migration of alkyl groups has been exploited by Feldman to generate nitrogen heterocycles via the addition of lithium sulfonamides to alkynyl(phenyl)iodonium salts such as **152** (Scheme 13).^{87a}

Scheme 13



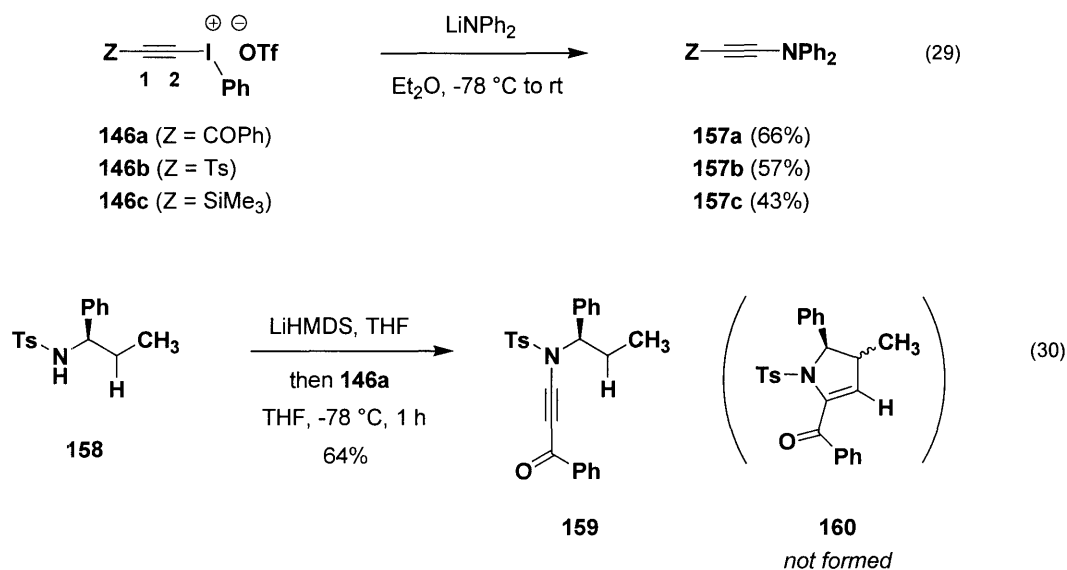
⁸⁴ For reviews of alkylidenecarbenes, see: (a) Knorr, R. *Chem. Rev.* **2004**, *104*, 3795. (b) Stang, P. J. *Methods of Organic Chemistry (Houben-Weyl)*, 4th ed.; 1989; Vol. E19b, pp 85–135.

⁸⁵ For an example, see: Margida, A. J.; Koser, G. F. *J. Org. Chem.* **1984**, *49*, 4703.

⁸⁶ Alkynylations of triphenylphosphine, triphenylarsine, and diphenyl sulfide, selenide, and telluride proceed smoothly when Z is an alkyl group. In these cases, rearrangement of the alkylidenecarbene may proceed via migration of the positively-charged onium group represented by “Nu” in **149** (eq 28). See refs 80–82.

⁸⁷ (a) Feldman, K. S.; Bruendl, M. M.; Schildknecht, K.; Bohnstedt, A. C. *J. Org. Chem.* **1996**, *61*, 5440. (b) Williamson, B. L.; Tykwinski, R. R.; Stang, P. J. *J. Am. Chem. Soc.* **1994**, *116*, 93. (c) Ochiai, M.; Kunishima, M.; Tani, S.; Nagao, Y. *J. Am. Chem. Soc.* **1991**, *113*, 3135. (d) Ochiai, M.; Kunishima, M.; Nagao, Y.; Fuji, K.; Shiro, M.; Fujita, E. *J. Am. Chem. Soc.* **1986**, *108*, 8281.

In 1994, Stang reported the first additions of lithium amides to alkynyl(phenyl)iodonium salts in a process leading to “push-pull” ynamines (Z = EWG) such as **157a–b** and silyl ynamine **157c** (eq 29).^{88,89} Two years later, Feldman extended this method to the synthesis of ynamides from lithium sulfonamides (eq 30).^{87a} Feldman speculated that “push-pull” ynamides such as **159** are generated from *ipso*-substitution at the alkynyl carbon of **146a** bearing the iodonium substituent (C-2). This alternative mechanism accounts for the absence of **160** which would be the product of addition at the C-1 carbon and subsequent alkylidenecarbene insertion into a vicinal carbon-hydrogen bond (*vide supra*).

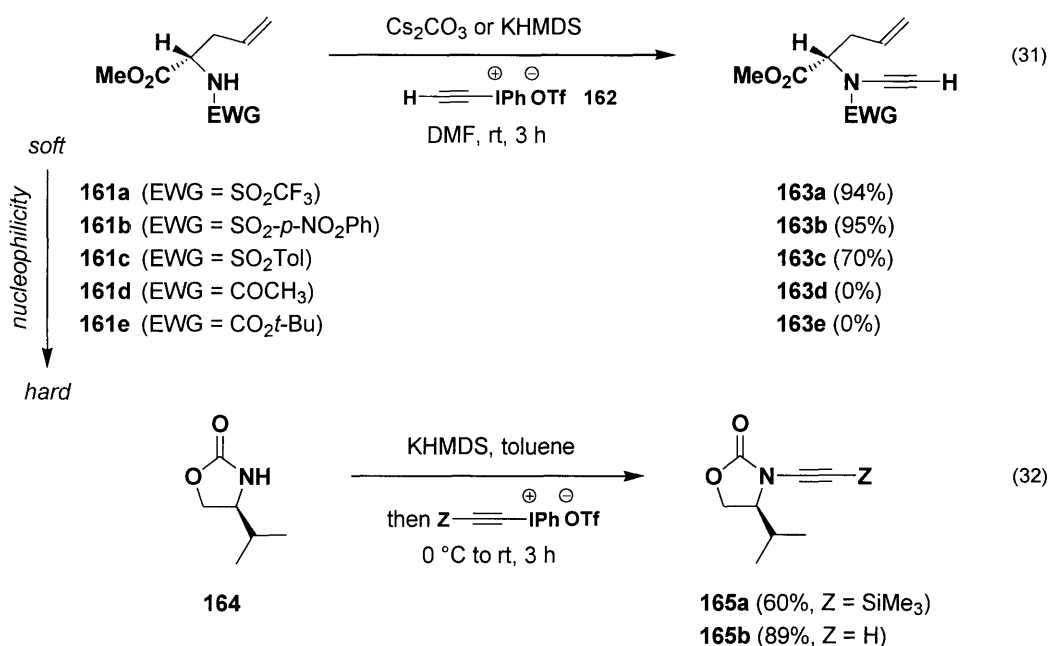


The availability of several types of ynamides from alkynyl(phenyl)iodonium salts prompted several groups to explore the use of these amido alkynes as synthetic building blocks. In particular, Witulski published a series of reports in which these iodonium reagents are used to prepare ynamides for Pauson-Khand reactions,^{57a,c,d} cycloadditions,¹⁶ alkyne trimerizations,⁵⁸ and other ring-forming processes.^{60a} Witulski explored the types of nitrogen nucleophiles which undergo alkynylation with iodonium salts and found that a variety of sulfonamides can participate in the desired reaction (eq 31).^{57d} Harder nitrogen nucleophiles, however, such as deprotonated acetamides and carbamates, react with the iodonium reagents via pathways that do

⁸⁸ Murch, P.; Williamson, B. L.; Stang, P. J. *Synthesis* **1994**, 1255.

⁸⁹ For subsequent syntheses of ynamines from the reaction of metalated benzotriazoles and alkynyl(phenyl)iodonium salts, see: (a) Kitamura, T.; Tashi, N.; Tsuda, K.; Fujiwara, Y. *Tetrahedron Lett.* **1998**, 39, 3787. (b) Kitamura, T.; Tashi, N.; Tsuda, K.; Chen, H.; Fujiwara, Y. *Heterocycles* **2000**, 52, 303.

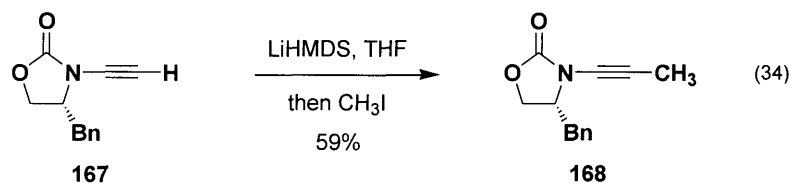
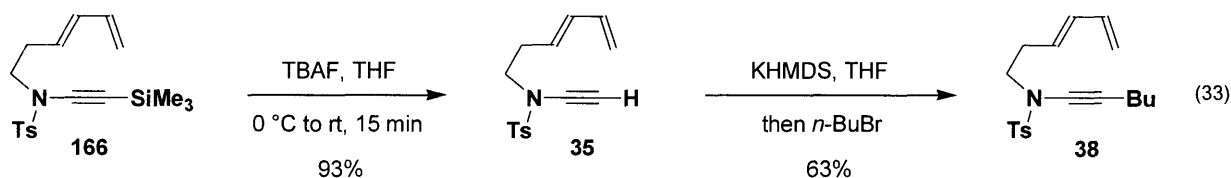
not furnish ynamide products (vide supra). Similarly, other researchers have reported the failure of lithiated lactams, oxazolidinones, and imidazolidinones to undergo alkynylation with alkynyl(phenyl)iodonium salts.^{50a} Interestingly, however, Cintrat found that the reaction of iodonium salts **146c** and **162** with the potassium derivatives of oxazolidinones can be used for the synthesis of ynamides such as **165a** and **165b**.^{55c}



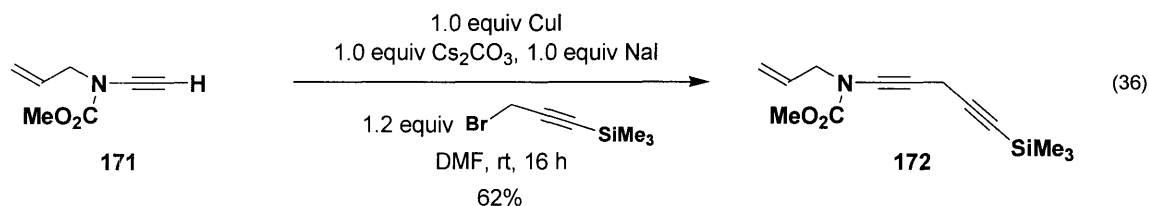
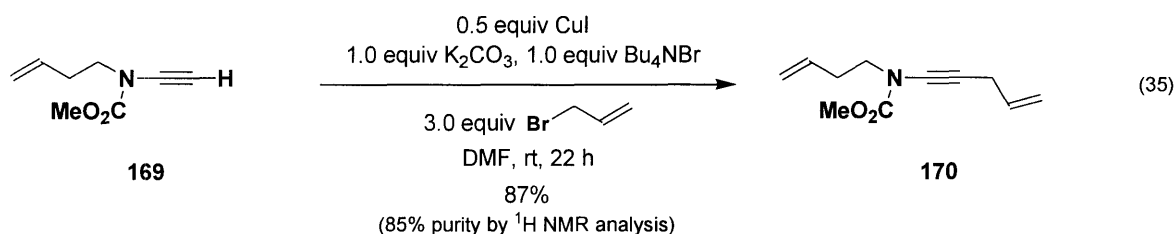
Elaboration of Terminal Ynamides via Alkylation or Transition-Metal-Catalyzed Coupling Reactions

As previously discussed, the requisite 1,2-shift of alkylidenecarbene intermediates is only a facile process when Z is a hydrogen atom or a trialkylsilyl or aryl group. As a result, alkynyl(phenyl)iodonium salts cannot directly provide ynamides with alkyl substituents on the acetylene. This limitation can be addressed by the alkylation of terminal ynamides as shown below. Witulski¹⁶ and Hsung⁹⁰ each have reported a single example of ynamide alkylation via deprotonation with a strong base and treatment with simple alkyl electrophiles (eq 33–34). In addition, current group member Xiao Yin Mak has converted terminal ynamide **169** to allyl substituted ynamide **170** according to the procedure developed by Jeffery for the copper-

⁹⁰ Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368.



catalyzed allylation of terminal alkynes (eq 35).⁹¹ Xiao Yin also applied the protocol of Spinella for the propargylation of acetylenes⁹² to the preparation of propargyl substituted ynamide **172** from terminal ynamide **171** (eq 36).



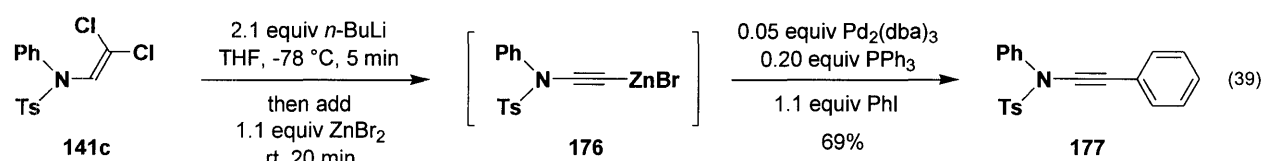
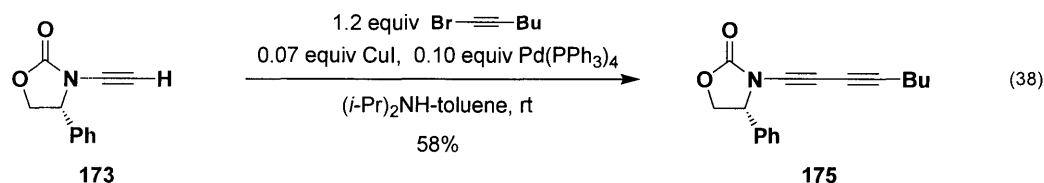
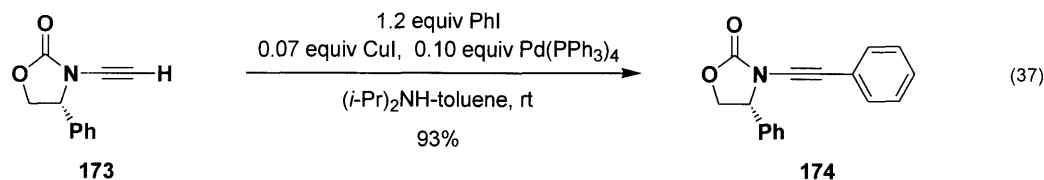
In 2004, Hsung reported the Sonogashira coupling of terminal ynamides such as **173** with various aryl and alkenyl halides (eq 37).⁹³ In this same communication, Hsung also reported a single example of coupling a terminal ynamide with an alkynyl bromide (eq 38).⁹⁴ The same year, Saá reported the Negishi coupling of zinc ynamides such as **176** with aryl halides for the preparation of aryl substituted ynamides such as **177**.⁷³ These zinc acetylides are generated from the elimination of dichloro enamide **141c** via metal-halogen exchange and trapping with ZnBr₂.

⁹¹ Jeffery, T. *Tetrahedron Lett.* **1989**, 30, 2225.

⁹² Caruso, T.; Spinella, A. *Tetrahedron* **2003**, 59, 7787.

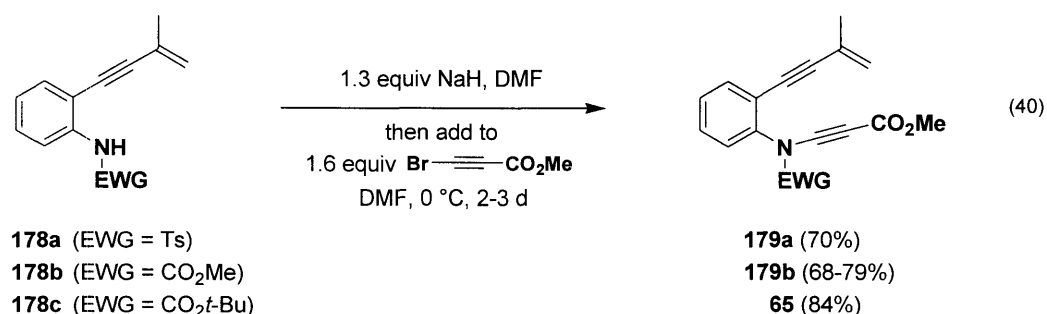
⁹³ Tracey, M. R.; Zhang, Y.; Frederick, M. O.; Mulder, J. A.; Hsung, R. P. *Org. Lett.* **2004**, 6, 2212.

⁹⁴ For the related Glaser coupling of terminal ynamides, see: Rodríguez, D.; Castedo, L.; Saá, C. *Synlett* **2004**, 377.



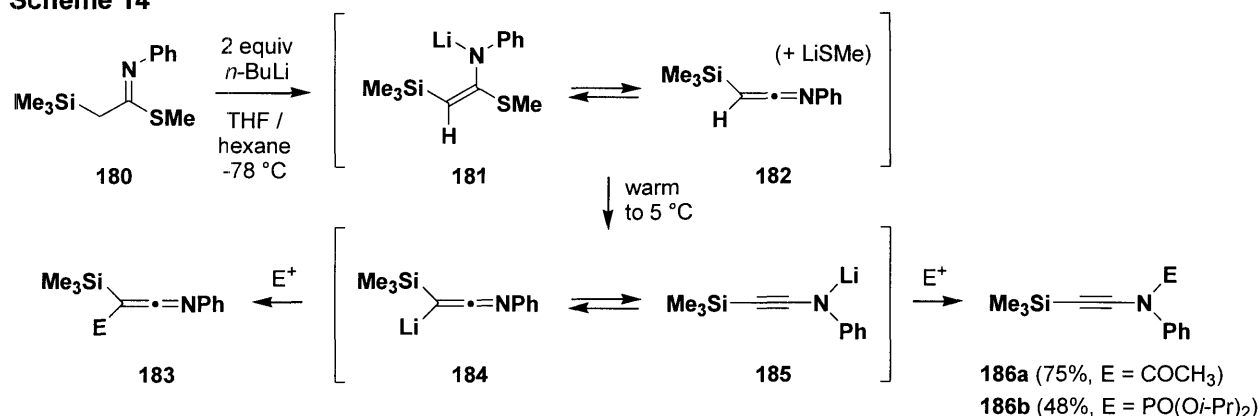
Other Strategies for the Synthesis of Ynamides

In addition to the isomerization, elimination, and alkynyl(phenyl)iodonium salt strategies discussed above, several less general methods for preparing ynamides were known when we began our studies. For example, former group member Brenda Palucki examined the reaction of metalated carbamates with methyl 3-bromopropiolate as a route to “push-pull” ynamides.^{33c} The addition of metalated amides to bromo alkynes, however, does not occur unless the acetylene is activated as a Michael acceptor through conjugation to an electron-withdrawing group.^{50a} The addition-elimination strategy shown below is related to the reactions reported by Stang and Feldman involving alkynyl(phenyl)iodonium salts (eq 29–30), but has the advantage of employing the more readily available alkynyl bromide.



Masson reported the synthesis of ynamides while attempting to prepare a series of *N*-phenyl (trialkylsilyl)ketenimines of type **183** from α -silyl imidothioester **180** (Scheme 14).⁹⁵ Deprotonation of **180** with an equivalent of *n*-BuLi at $-78\text{ }^{\circ}\text{C}$ leads to lithium enamide **181** which exists in equilibrium with **182** via the loss of lithium thiomethoxide. Warming to $5\text{ }^{\circ}\text{C}$ effects deprotonation by a second equivalent of base to generate C-lithiated ketenimine **184** in equilibrium with *N*-lithiated ynamine **185**. Quenching the reaction mixture with excess acetyl chloride or diisopropyl chlorophosphate furnishes ynamides **186a** and **186b** (instead of the desired ketenimines) via acetylation or phosphorylation of the nitrogen.

Scheme 14



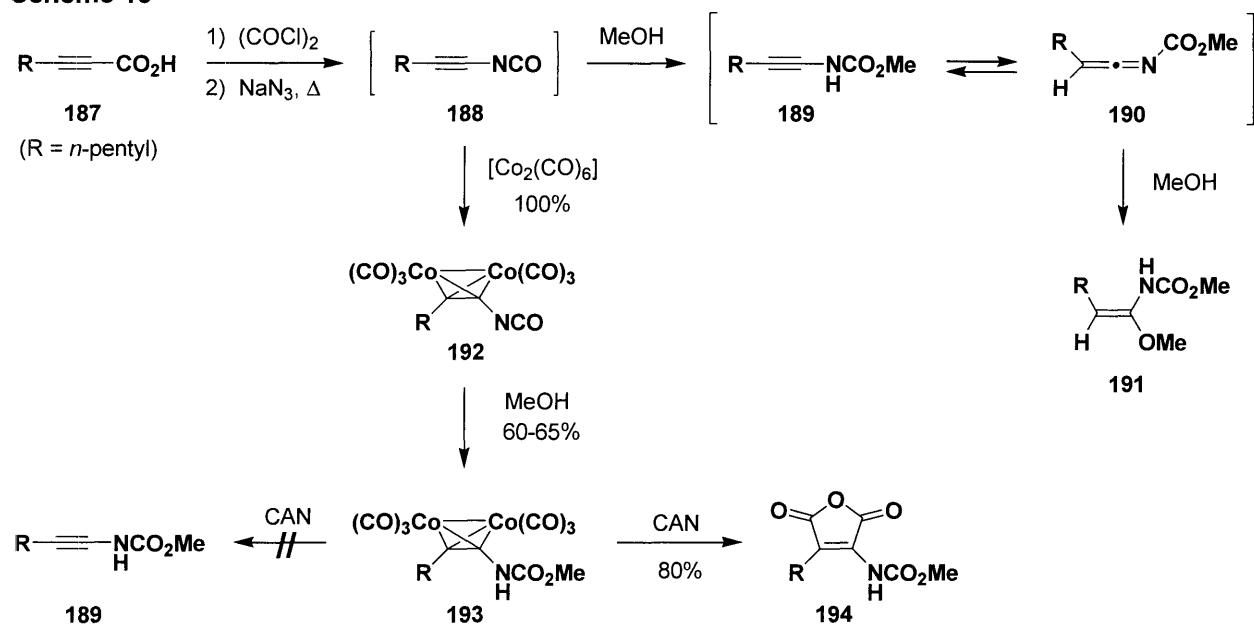
Finally, an interesting potential approach to the synthesis of ynamides involves the Curtius rearrangement of alkynoyl azides followed by alcoholysis of the resulting isocyanates. Unfortunately, Chen could not isolate the desired ynamide **189** from the addition of methanol to alkynyl isocyanate **188** (Scheme 15).^{96,97} Instead, Chen obtained **191** after trapping the ketenimine **190** formed by tautomerization of the initial ynamide product with a second equivalent of alcohol. Chen tried to circumvent this problem by first protecting alkynyl isocyanate **188** as the cobalt complex **192** before alcoholysis. Treatment of the cobalt complex **192** with methanol provides the carbamate **193** in moderate yield. Deprotection of the alkyne with ceric ammonium nitrate, however, fails to afford the desired ynamide **189** but rather leads to maleic anhydride derivative **194**.

⁹⁵ Fromont, C.; Masson, S. *Tetrahedron* **1999**, 55, 5405.

⁹⁶ Schottelius, M. J.; Chen, P. *Helv. Chim. Acta* **1998**, 81, 2341.

⁹⁷ For earlier syntheses of alkynyl isocyanates via Curtius rearrangement, see: (a) Curtius, T.; Kenngott, E. *J. Prakt. Chem.* **1926**, 112, 314. (b) Boyer, J. H.; Selvarajan, R. *J. Am. Chem. Soc.* **1969**, 91, 6122.

Scheme 15



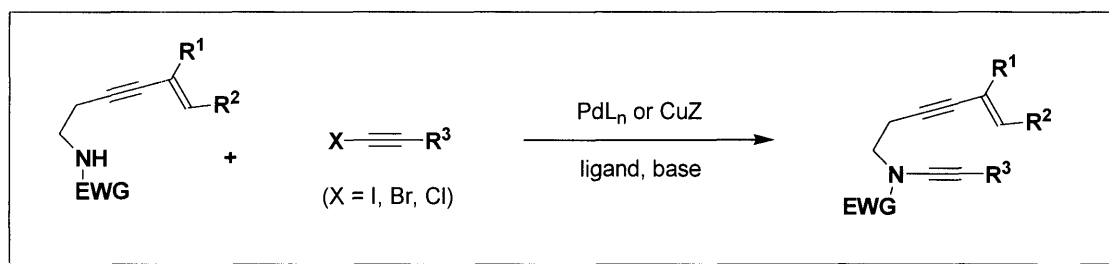
Summary

There were several known strategies for the synthesis of ynamides when we first began investigating these compounds as substrates for our enyne cycloaddition reactions. Despite the availability of methods involving the isomerization of propargyl amides and the elimination of halo enamides, we were interested in exploring more convergent and synthetically attractive routes to ynamides that would involve the alkynylation of a nitrogen nucleophile. Alkynyl(phenyl)iodonium salts react with some nitrogen nucleophiles in the desired fashion to generate ynamides bearing silyl, aryl, or hydrogen substituents; however, our proposed method for the synthesis of indolines and indoles via enyne cycloaddition requires an alkynylation strategy that can provide access to ynamides with a much wider range of substitution on the acetylene. Our efforts to design and develop such a strategy are discussed in the next chapter.

Chapter 4

Ynamides via Copper-Mediated N-Alkynylation Reactions: Coupling of Amide Derivatives with Alkynyl Halides

The limitations of the methodology for the synthesis of ynamides discussed in the previous chapter prompted us to consider alternative and potentially more general approaches to the synthesis of the ynamides required for our cycloaddition studies. Inspired by recent advances in transition-metal-catalyzed carbon-nitrogen bond formation, we turned our attention to the unprecedented coupling of amide derivatives with readily available alkynyl halides. We envisioned that this strategy would provide access to a wide range of ynamides with various substituents on the acetylene.



Synthesis of Arylamines and Enamines via Coupling Reactions of Aryl and Vinyl Halides

Palladium-⁹⁸ and copper-catalyzed⁹⁹ carbon-nitrogen bond-forming reactions involving the coupling of amines with aryl halides or sulfonates are well-established and powerful methods in organic synthesis. The original copper-mediated amination (Ullmann reaction)¹⁰⁰ and amidation (Goldberg reaction)¹⁰¹ of halo arenes predate palladium-catalyzed methods by several decades. These traditional Ullmann and Goldberg reactions often require stoichiometric amounts

⁹⁸ For reviews, see: (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, 219, 131. (b) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed., Wiley-Interscience: New York, 2002; Vol. 1, pp 1051–1096. (c) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, 576, 125.

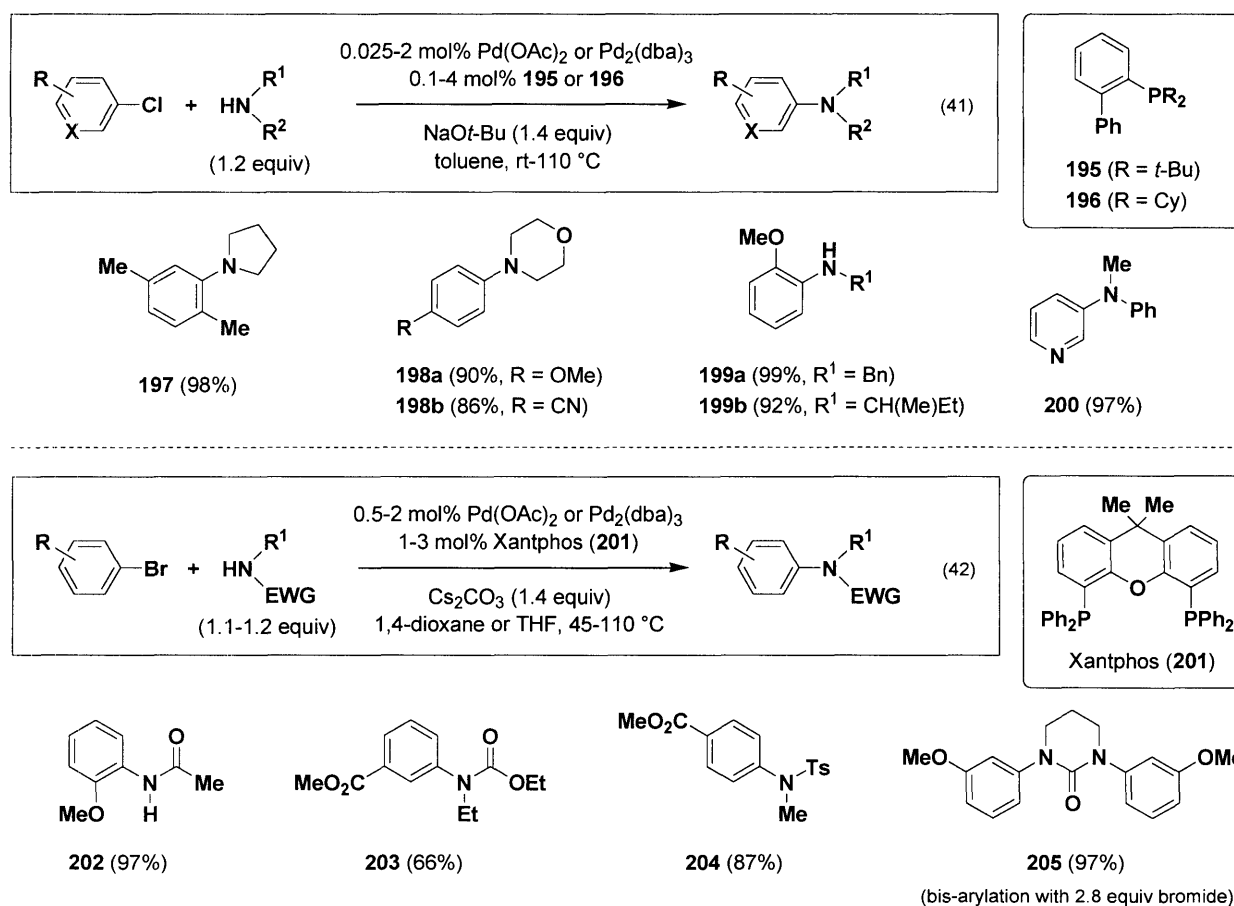
⁹⁹ For reviews, see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, 248, 2337. (b) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428. (c) Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, 42, 5400.

¹⁰⁰ Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, 36, 2382.

¹⁰¹ Goldberg, I. *Ber. Dtsch. Chem. Ges.* **1906**, 39, 1691.

of copper, high temperatures (typically above 150 °C), and polar solvents such as DMF, DMSO, and HMPA.¹⁰²

Recent improvements by Buchwald¹⁰³ and Hartwig¹⁰⁴ have revolutionized methodology for carbon-nitrogen bond formation. Independent and concurrent research efforts by these laboratories have explored various palladium catalysts, ligands, bases, and solvents that effect the amination and amidation of aryl halides and sulfonates under relatively mild conditions. Some representative protocols developed by Buchwald for the palladium-catalyzed arylation of amines^{103c} and amide derivatives^{103d} are shown below.

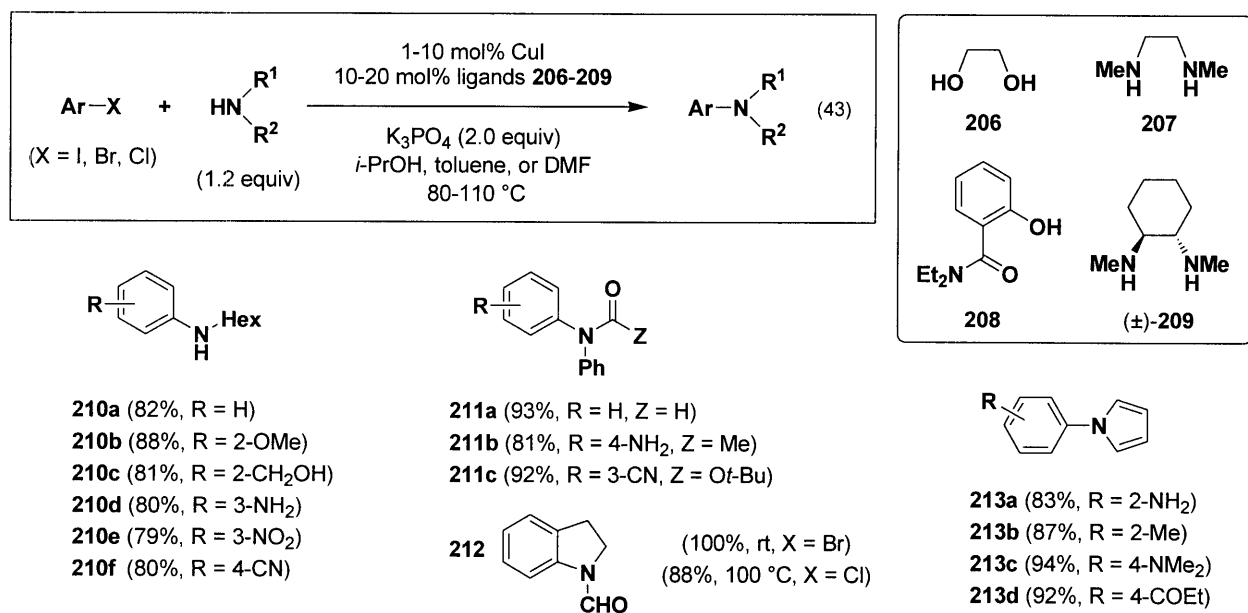


¹⁰² For a review of traditional Ullmann and Goldberg conditions, see: Lindley, J. *Tetrahedron* **1984**, *40*, 1433.

¹⁰³ For an overview of palladium-catalyzed N-arylations developed by Buchwald, see: (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (b) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144. (c) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158. (d) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043. (e) Anderson, K. W.; Mendez-Perez, M.; Priego, J.; Buchwald, S. L. *J. Org. Chem.* **2003**, *68*, 9563. Also see ref 98.

¹⁰⁴ For an overview of palladium-catalyzed N-arylations developed by Hartwig, see: (a) Hartwig, J. F. *Synlett* **1997**, 329. (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369. (c) Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2003**, *68*, 2861. Also see ref 98.

In addition to methods for the palladium-catalyzed coupling of amines and amide derivatives with aryl halides and sulfonates, Buchwald also developed complementary copper-catalyzed protocols which employ bidentate ligands and are greatly superior to the conditions of the classical Ullmann and Goldberg reactions.^{105,106} Copper is often an attractive alternative to palladium for several reasons. Copper catalysts generally have greater functional group compatibility than palladium reagents¹⁰⁷ and can be easier to separate from polar reaction products. Copper salts are also usually less expensive than palladium reagents. Since the traditional copper-mediated aminations and amidations require stoichiometric amounts of metal, polar ligating solvents, and high temperatures often in excess of 150 °C, Buchwald explored chelating ligands **206–209** which coordinate to copper and activate the catalyst for couplings at milder temperatures in hydrocarbon solvents. Illustrated below are some representative examples of copper-catalyzed N-arylations developed in the Buchwald laboratories.



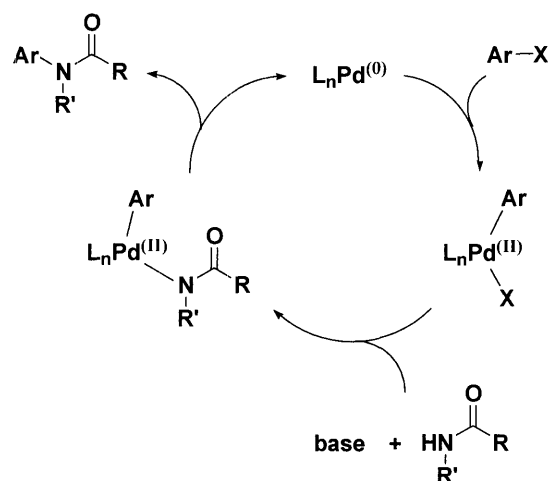
¹⁰⁵ For an overview of copper-catalyzed N-arylations developed by Buchwald, see: (a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. (b) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581. (c) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421. (d) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684. (e) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793. (f) Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578.

¹⁰⁶ For examples of the accelerating effect of ligands for copper-catalyzed N-arylations by other groups, see: (a) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459. (b) Goodbrand, H. B.; Hu, N.-X. *J. Org. Chem.* **1999**, *64*, 670. (c) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315. (d) Kang, S.-K.; Kim, D.-H.; Park, J.-N. *Synlett* **2002**, 427. (e) Kelkar, A. A.; Patil, N. M.; Chaudhari, R. V. *Tetrahedron Lett.* **2002**, *43*, 7143.

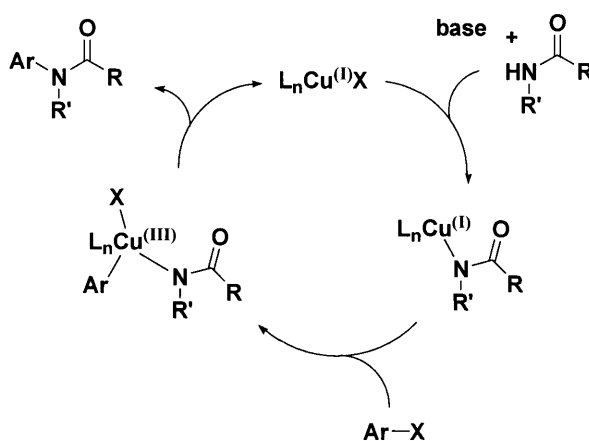
¹⁰⁷ For a discussion of limitations regarding the functional group compatibility of palladium-catalyzed C-N bond-forming reactions, see: Harris, M. C.; Huang, X.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 2885.

Buchwald proposes the mechanisms shown below for these palladium- and copper-catalyzed carbon-nitrogen bond-forming reactions.¹⁰⁸ The palladium-catalyzed N-arylation of amides is believed to proceed via oxidative addition of the aryl halide (or sulfonate) to the $L_nPd(0)$ complex. Metathesis of amide for halide (or sulfonate) generates an aryl amido Pd(II) intermediate, and subsequent reductive elimination provides the aniline product and regenerates the $L_nPd(0)$ catalyst. In contrast, amidations catalyzed by copper(I) salts are believed to proceed via copper-nitrogen bond formation *prior* to oxidative addition of the aryl halide (or sulfonate). Reductive elimination of a transient copper(III) intermediate then furnishes the aniline and regenerates the copper(I) catalyst.

Scheme 16



Scheme 17

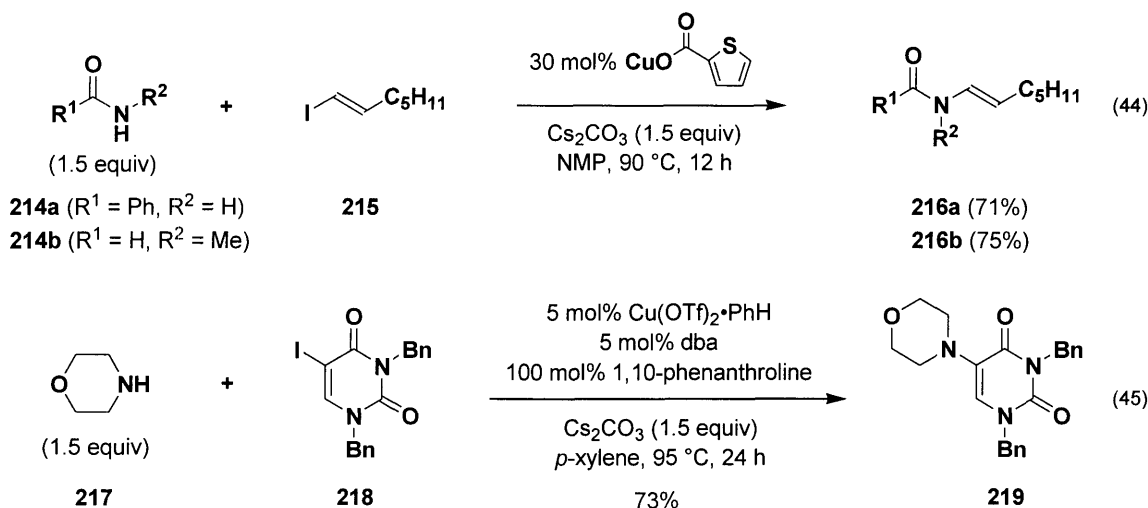


Palladium- and copper-catalyzed aminations and amidations of non-aromatic halides and sulfonates have received far less attention than reactions with aromatic derivatives. When we began to explore the synthesis of ynamides via couplings of amide derivatives, reactions involving alkynyl halides were not known, although there were scattered reports of the synthesis of enamines and enamides via couplings with alkenyl halides.¹⁰⁹ In 2000, Porco reported the amidation of alkenyl halides with catalytic amounts of copper(I) 2-thiocarboxylate as a new

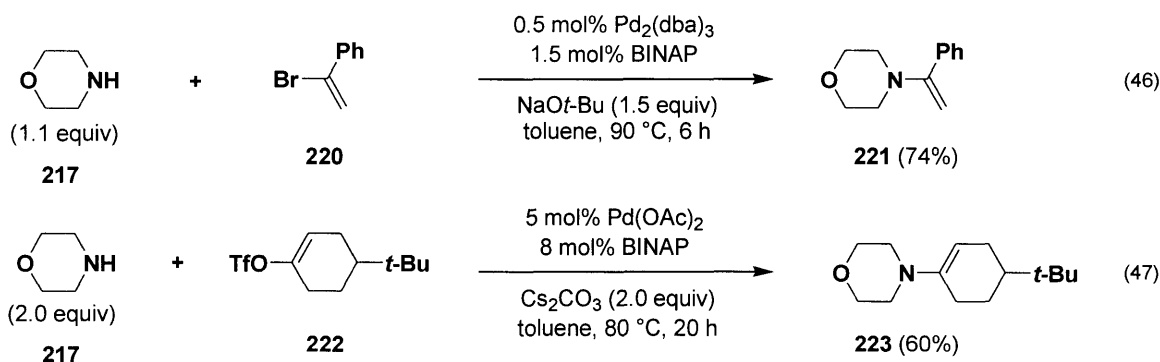
¹⁰⁸ For mechanistic discussion of Pd-catalyzed N-arylations, see ref 103a. For mechanistic discussion of Cu-catalyzed N-arylations, see ref 105c.

¹⁰⁹ For a review of enamine and enamide syntheses, see: Dehli, J. R.; Legros, J.; Bolm, C. *Chem. Commun.* **2005**, 973.

approach to the assembly of enamides for the synthesis of salicylate macrolides (eq 44).¹¹⁰ A year later, Arterburn reported the copper-catalyzed aminations of iodouracil derivatives (eq 45).¹¹¹ Concurrent reports in 2002 by Barluenga and Willis applied the palladium-catalyzed



Buchwald-Hartwig amination conditions to the synthesis of enamines from alkenyl bromides¹¹² and triflates¹¹³ (eq 46–47).¹¹⁴ These N-alkenylation methods and previously discussed N-arylation protocols provided us with direction for our early investigations into the synthesis of ynamides via coupling of amide derivatives with *alkynyl* halides.



¹¹⁰ Shen, R.; Porco, J. A., Jr. *Org. Lett.* **2000**, 2, 1333.

¹¹¹ Arterburn, J. B.; Pannala, M.; Gonzalez, A. M. *Tetrahedron Lett.* **2001**, 42, 1475.

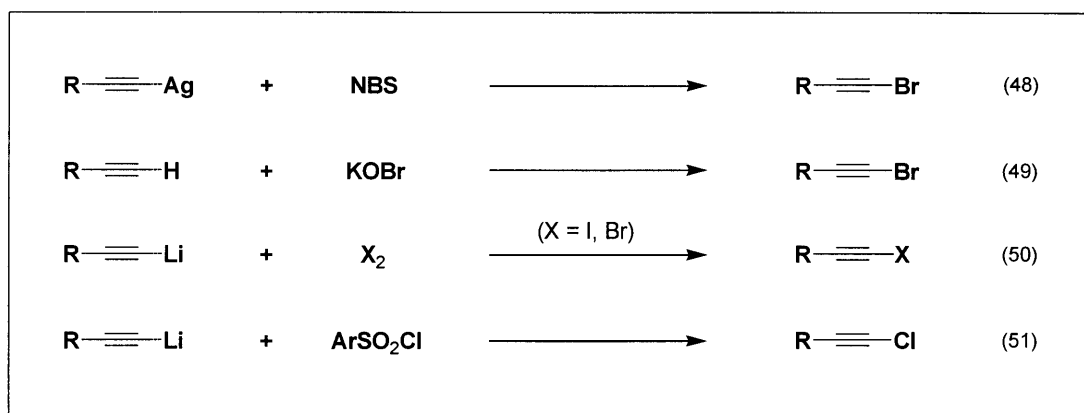
¹¹² Barluenga, J.; Fernández, M. A.; Aznar, F.; Valdés, C. *Chem. Commun.* **2002**, 2362.

¹¹³ Willis, M. C.; Brace, G. N. *Tetrahedron Lett.* **2002**, 43, 9085.

¹¹⁴ For more recent copper- or palladium-catalyzed N-alkenylations, see: (a) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, 5, 3667 and ref 109. For later examples of related copper-catalyzed N-allenylations, see: (b) Trost, B. M.; Stiles, D. T. *Org. Lett.* **2005**, 7, 2117. (c) Shen, L.; Hsung, R. P.; Zhang, Y.; Antoline, J. E.; Zhang, X. *Org. Lett.* **2005**, 7, 3081.

Preparation of 1-Haloacetylenes for Coupling Reactions

1-Haloacetylenes are versatile substrates in organic synthesis and there are several convenient and efficient methods for the preparation of these compounds from the corresponding terminal alkynes.¹¹⁵ Equations 48–51 illustrate the various reagents we employed for the synthesis of alkynyl iodides, bromides, and chlorides. This section will discuss our results concerning the preparation of 1-haloacetylenes for our coupling reactions.

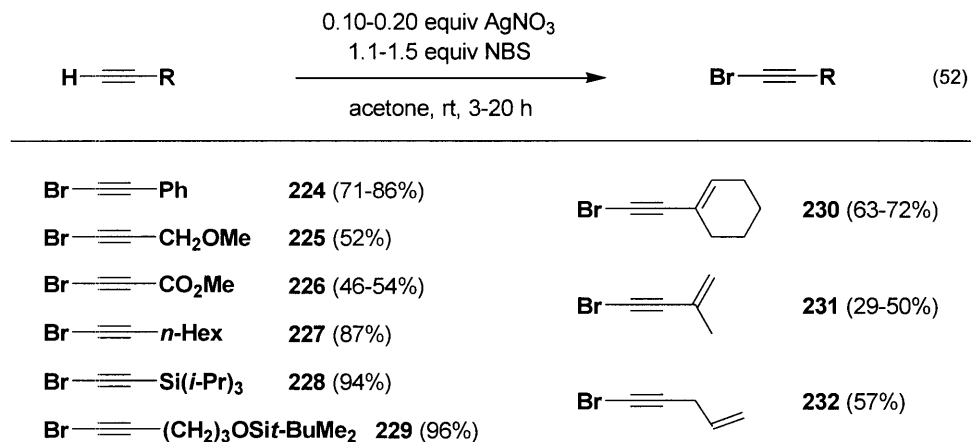


We synthesized several 1-bromoacetylenes from commercially available terminal alkynes¹¹⁶ using catalytic silver nitrate and *N*-bromosuccinimide according to the general method of Hofmeister (eq 52).¹¹⁷ This protocol generates nucleophilic silver acetylides in situ via π -coordination of the silver cation to the terminal alkyne and deprotonation by the basic nitrate anion. This mild bromination protocol is compatible with a variety of acetylenes. The bromo alkynes (and other halo alkynes discussed in this section) usually were purified by distillation at reduced pressures and slightly elevated temperatures, as these compounds are somewhat sensitive to heating. Bromo alkyne **231** is particularly sensitive to polymerization and we isolated this compound in lower yield than its non-conjugated isomer **232**. To minimize decomposition on prolonged storage, we routinely stored the haloacetylenes frozen in benzene solution at $-20\text{ }^\circ\text{C}$.

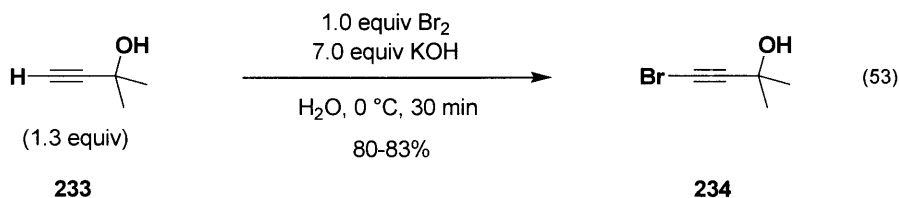
¹¹⁵ For reviews of the chemistry of 1-haloacetylenes, see: (a) Hopf, H.; Witulski, B. In *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, 1995; pp 33–66. (b) Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier: New York, 1988.

¹¹⁶ The terminal alkyne precursor to **229** was available via silylation of 5-hexyn-1-ol.

¹¹⁷ Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R. *Angew. Chem. Int. Ed.* **1984**, 23, 727.



An alternative route to 1-bromoacetylenes involves the treatment of terminal acetylenes with potassium hypobromite.^{115,118} This method is particularly well-suited for the preparation of polar alkynyl bromides. The protocol we used for the synthesis of **234** generates potassium hypobromite in situ from the slow addition of bromine to an aqueous solution of alkyne and potassium hydroxide.



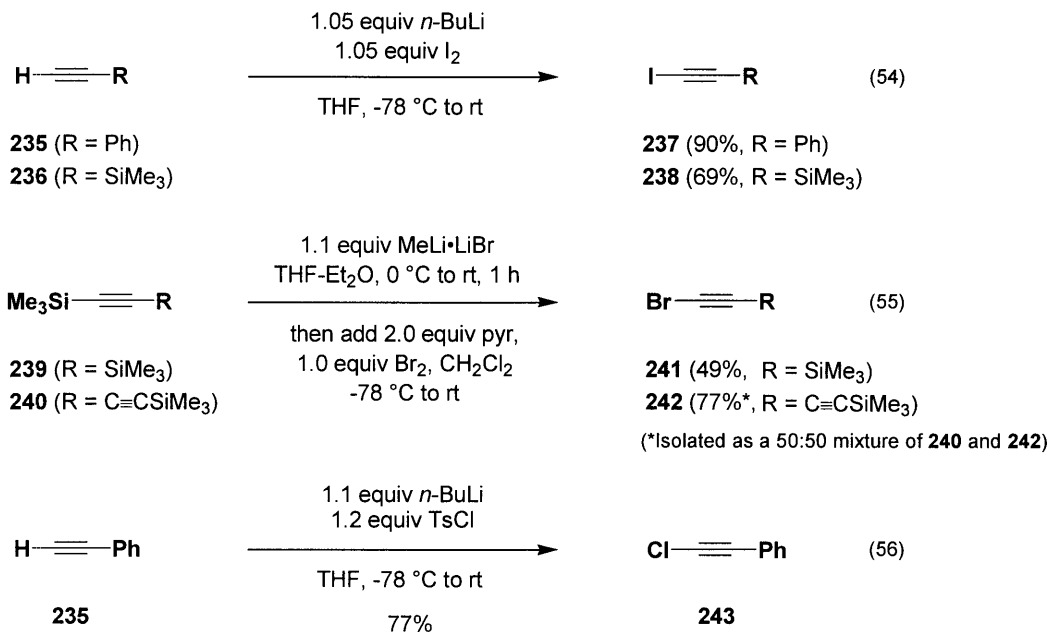
The reaction of lithium acetylides with iodine or bromine provides another route to 1-haloacetylenes.¹¹⁵ We used this approach to synthesize alkynyl iodides **237** and **238** and bromides **241**¹¹⁹ and **242**.¹²⁰ The requisite alkynyllithium reagents were prepared by deprotonation of terminal acetylenes (eq 54) or via transmetalation of alkynyl silicates to lithium (eq 55). The slow addition of iodine or bromine to solutions of lithium acetylide cooled at low temperature provided 1-iodo and 1-bromoacetylenes without halogenation of the triple bond. While the analogous reaction of alkynyllithiums with chlorine provides 1-chloroacetylenes, it

¹¹⁸ For examples of this method, see: Marino, J. P.; Nguyen, H. N. *J. Org. Chem.* **2002**, 67, 6841.

¹¹⁹ Prepared according to the procedure of Miller, J. A.; Zweifel, G. *Synthesis* **1983**, 128.

¹²⁰ Prepared according to the procedure of Basak, S.; Srivastava, S.; le Noble, W. J. *J. Org. Chem.* **1987**, 52, 5095.

was more convenient to use toluenesulfonyl chloride as a chlorinating agent for the synthesis of **243** (eq 56).^{115,121}



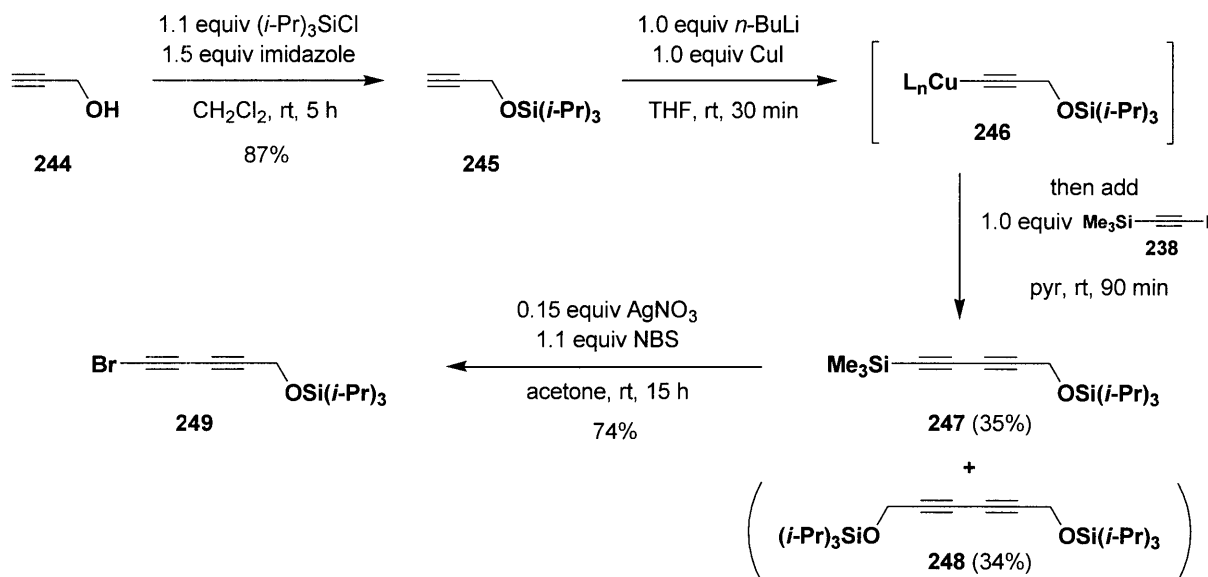
Whereas bromo diyne **242** was prepared directly from commercially available **240**, the synthesis of more complex bromo diynes required several synthetic steps. Scheme 18 shows the reaction sequence for the preparation of bromo diyne **249**. Silylation of **244** protected the propargyl alcohol, and deprotonation of **245** followed by treatment with copper(I) iodide generated alkynylcopper **246** according to the procedure of Zweifel.¹¹⁹ Subsequent addition of iodo(trimethylsilyl)acetylene furnished the desired diyne **247** via modified Cadiot-Chodkiewicz coupling¹²² in modest yield. Diyne **248** was also isolated in significant yield and is likely the product of an undesired Glaser coupling¹²² of two copper acetylides. The silyl diyne **247** was converted to bromo diyne **249** with silver nitrate and *N*-bromosuccinimide. This reaction likely proceeds via π -coordination of the silver cation to the alkyne followed by cleavage of the silyl group by water which is present in acetone in trace amounts.¹²³

¹²¹ For examples of this method in the literature, see: Bartmettler, P.; Hansen, H.-J. *Helv. Chim. Acta* **1990**, *73*, 1515.

¹²² For a review, see: Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 3, pp 551–561 and references therein.

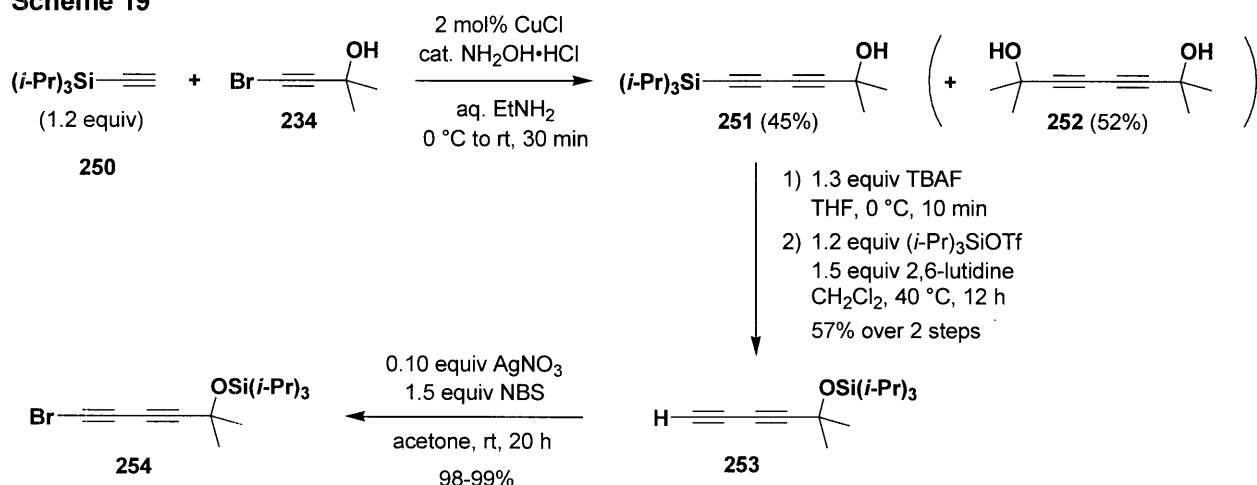
¹²³ This reaction is facilitated by the addition of water to the reaction solvent. See: Shen, R.; Lin, C. T.; Bowman, E. J.; Bowman, B. J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 7889.

Scheme 18



The related bromo diyne **254** was prepared as shown in Scheme 19. The Cadiot-Chodkiewicz coupling of (triisopropylsilyl)acetylene (**250**) and alkynyl bromide **234** according to the protocol of Marino¹¹⁸ provided diyne **251** and the undesired homocoupling product **252**.¹²⁴ Desilylation of **251**¹²⁵ followed by protection of the alcohol led to **253**, and bromination using the general method of Hofmeister furnished bromo diyne **254**.

Scheme 19

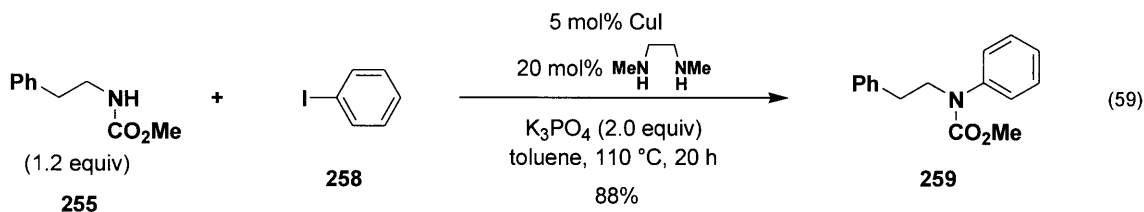
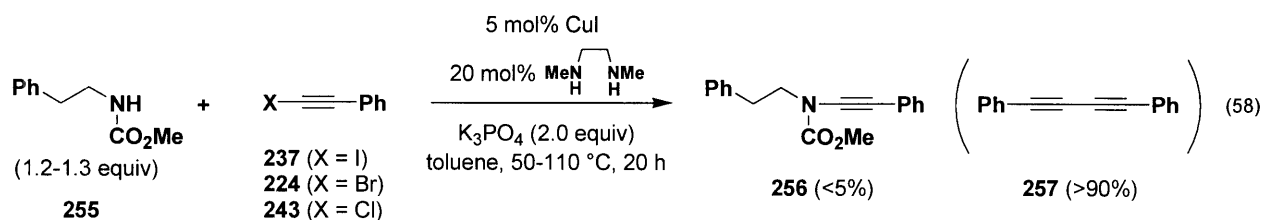
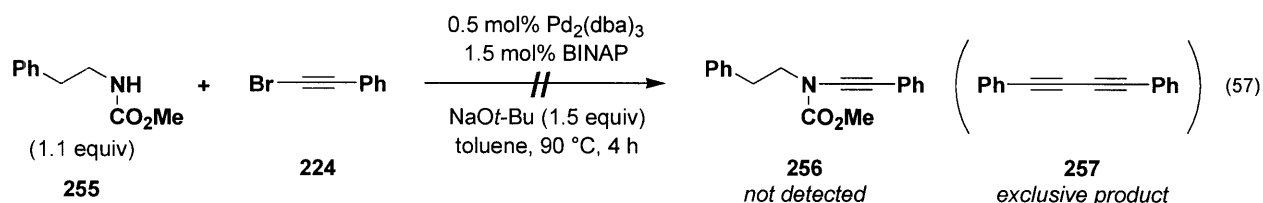


¹²⁴ The diyne from the homocoupling of **250** was also detected by ^1H NMR analysis of the crude reaction mixture.

¹²⁵ Conditions that convert (trimethylsilyl)acetylenes to bromo alkynes (cat. AgNO_3 , NBS, wet acetone), do not effect the analogous conversion of (triisopropylsilyl)acetylenes. For the direct synthesis of bromo alkynes from (triisopropylsilyl)acetylenes using stoichiometric AgF and NBS, see: Kim, S.; Kim, S.; Lee, T.; Ko, H.; Kim, D. *Org. Lett.* **2004**, 6, 3601.

Coupling of 1-Haloacetylenes with Amide Derivatives

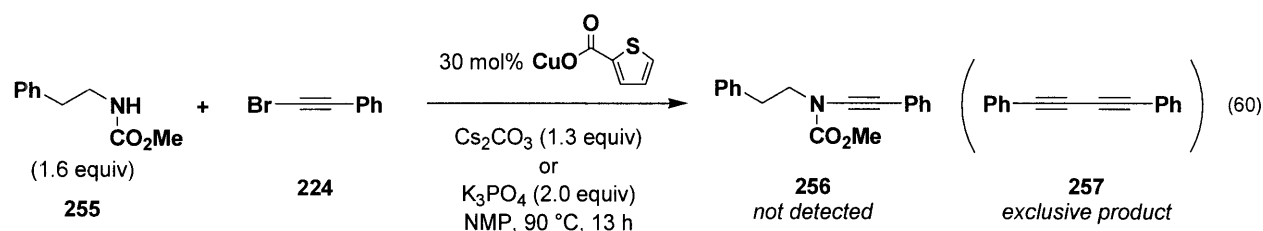
Encouraged by the palladium- and copper-catalyzed amidations of aryl and alkenyl halides discussed earlier in this chapter, we turned our attention to the unprecedented coupling of amide derivatives with alkynyl halides.¹²⁶ Initial results were disappointing. As shown below, application of the palladium-^{103b} and copper-catalyst^{105c} systems developed by Buchwald to the coupling of acyclic carbamates with 1-iodo- or 1-bromo-2-phenylacetylene gave only trace amounts of the desired ynamide, with the predominant product being the 1,3-diyne generated from the homocoupling of the alkynyl halide. We thought that 1-chloro-2-phenylacetylene might be less prone to homocoupling; however, reactions with the alkynyl chloride also led exclusively to diyne **257**. In comparison, control experiments using the same copper-catalyzed conditions for the coupling of the same acyclic carbamate to an aryl iodide generated the expected aniline in high yield.



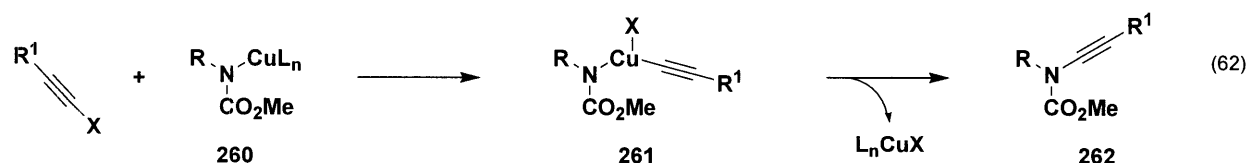
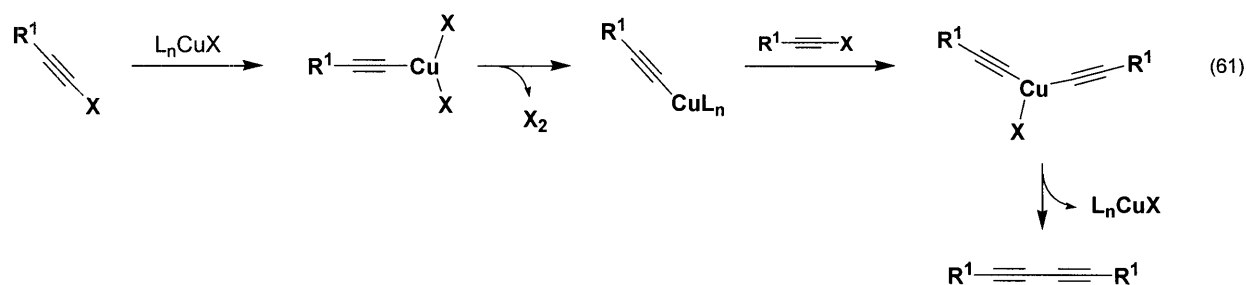
We next examined the synthesis of ynamides using the catalyst system developed by Porco for the amidation of alkenyl halides. Porco had noted that copper(I) thiophene-2-

¹²⁶ For two early reports of the observation of copper-promoted formation of ynamines and ynamides from reactions of amine derivatives with *terminal* alkynes, see: (a) Peterson, L. I. *Tetrahedron Lett.* **1968**, 9, 5357. (b) Balsamo, A.; Macchia, B.; Macchia, F.; Rossello, A.; Domiano, P. *Tetrahedron Lett.* **1985**, 26, 4141.

carboxylate leads to more efficient coupling than CuI, and that *N*-methyl-2-pyrrolidinone (NMP) is a suitable solvent and ligand for the reaction.¹¹⁰ Unfortunately, these conditions promoted the homocoupling of bromo alkyne **224** and did not afford any of the desired ynamide (eq 60).



The dimerization of 1-haloacetylenes by transition metals is well-documented;^{122,127} however, the mechanism of these reactions is not completely understood. It is believed that palladium- and copper-catalyzed homocoupling pathways begin with oxidative addition of the alkynyl halide to the metal and generate the diyne after reductive elimination of a (bis)alkynyl metal species as shown in eq 61. In order for the desired N-alkynylation to compete with this homocoupling process, it is necessary that the alkynyl halide react with our copper(I) amide intermediate (e.g., **260**, eq 62) fast enough to compete with the alternative reactions of the alkynyl halide with L_nCuX and R¹-C≡C-CuL_n (eq 61). We speculated that in the presence of bases such as K₃PO₄, Cs₂CO₃, and NaO*t*-Bu, we were not generating a sufficient concentration of **260**. We therefore turned our attention to protocols in which complete conversion of the



¹²⁷ For recent examples, see: (a) Setzer, W. N.; Gu, X.; Wells, E. B.; Setzer, M. C.; Moriarity, D. M. *Chem. Pharm. Bull.* **2000**, *48*, 1776. (b) Damle, S. V.; Seomoon, D.; Lee, P. H. *J. Org. Chem.* **2003**, *68*, 7085.

amide substrate to its copper derivative was carried out *prior* to addition of the alkynyl halide. We believed that preforming the copper amide **260** would maximize the rate of its reaction with the 1-haloacetylene as shown in eq 62, allowing the amidation to more effectively compete with the reaction of the alkynyl halide with copper salts in pathways leading to homodimer side products. Encouraging with regard to this plan was a previous report by Ogawa for the analogous formation of enamides from preformed copper amides and alkenyl halides.¹²⁸ However, the Ogawa coupling required a large excess of copper amide and elevated temperatures (130 °C) in HMPA, and we were interested in developing a protocol that would effect the alkynylation of copper amide **260** under milder conditions, particularly for the preparation of thermally sensitive cycloaddition substrates.¹²⁹

The results of our systematic investigation of reaction variables using carbamate **255** as the test substrate are outlined in Table 2. Potassium hexamethyldisilazide (in THF solution) and copper(I) iodide were efficient reagents for the conversion of **255** to its copper derivative, and we found it convenient to add the alkynyl halides as stock solutions in benzene.¹³⁰ Both acetylenic iodides and bromides participate in the alkynylation at *room temperature*, and chloro alkynes also undergo amidation but only upon heating and then in poor yield (entries 1–3). As expected, somewhat improved yields are observed when two equivalents of alkynyl halides are employed to compensate for losses due to homocoupling (compare entries 2 and 9); however, the reaction is very sluggish when a larger excess of halide is used (entry 12). Interestingly, pyridine proved to be the most effective solvent for this alkynylation reaction, clearly superior to the toluene-diamine ligand system (entry 11) employed by Buchwald^{105c} in his amidation studies. Under our optimal conditions (entry 9), the desired ynamide **256** was obtained in 67% yield beginning with 200 mg of carbamate, with the yield increasing to 76% when the reaction was carried out on a multigram scale. In the final reaction mixture, the ratio by volume of pyridine to benzene (from the bromo alkyne solution) to THF (from the KHMDS solution) is approximately 60:30:10. In subsequent studies, current group member Lucy Kohnen has found that a certain volume of pyridine can be replaced by additional THF without adversely affecting the yield of coupling.¹³¹

¹²⁸ Ogawa, T.; Kiji, T.; Hayami, K.; Suzuki, H. *Chem. Lett.* **1991**, 1443.

¹²⁹ The development and scope of our ynamide synthesis has appeared in the following publication: Dunetz, J. R.; Danheiser, R. L. *Org. Lett.* **2003**, 5, 4011.

¹³⁰ Control experiments in which the alkynyl halide was added neat revealed that the yield of coupling product is not affected by the presence of benzene in the reaction mixture.

¹³¹ Kohnen, A. L.; Dunetz, J. R.; Danheiser, R. L. *Org. Synth.* Manuscript in preparation.

When the alkynyl halide is added as a solution in THF under these modified conditions, the solvent ratio of THF to pyridine is 75:25 in the final reaction mixture. Finally, the yields in these reactions directly reflect the degree of conversion of carbamate to ynamide; yields are near quantitative based on the recovery of unreacted carbamate.¹³²

Table 2. Optimization of Alkynylation Conditions^a

<div style="display: flex; align-items: center; justify-content: center;"> <div style="text-align: center;"> $\text{Ph}-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CO}_2\text{Me}$ 255 </div> <div style="text-align: center; margin: 0 20px;"> $\xrightarrow[\text{then add } \text{X}-\text{C}\equiv\text{C}-\text{Ph}]{\begin{array}{c} 1.0 \text{ equiv base} \\ 1.0 \text{ equiv CuZ} \\ \text{solvent, rt, 2 h} \end{array}}$ </div> <div style="text-align: center;"> $\text{Ph}-\text{CH}_2-\text{CH}_2-\text{N}(\text{C}\equiv\text{C}-\text{Ph})-\text{CO}_2\text{Me}$ 256 </div> </div>					
entry	base	CuZ	solvent ^b	alkyne equiv, X	yield (%) ^c
1	KHMDS	CuI	pyr	1.0, I	44
2	KHMDS	CuI	pyr	1.0, Br	48
3	KHMDS	CuI	pyr ^d	1.0, Cl	23
4	KHMDS	CuI	DMF	1.0, Br	26
5	<i>n</i> -BuLi	CuI	pyr	1.0, Br	0
6	<i>n</i> -BuLi	CuI	DMSO	1.0, Br	20
7	<i>n</i> -BuLi	CuTC ^e	DMSO	1.0, Br	24
8	KHMDS	CuI	pyr	0.6, Br	40 ^f
9	KHMDS	CuI	pyr	2.0, Br	67^g
10	KHMDS	CuCN	pyr	2.0, Br	41
11	KHMDS	CuI	tol, diamine ^h	2.0, Br	40
12	KHMDS	CuI	pyr	5.0, Br	28 ⁱ

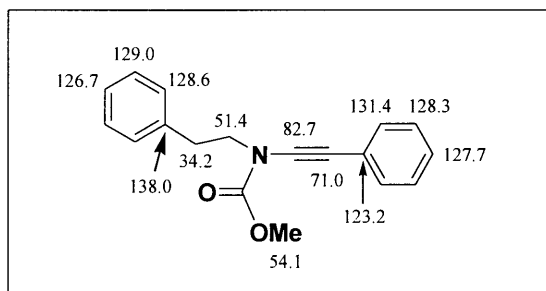
^a All reactions were carried out at rt for 20 h unless otherwise indicated. Concentration of **255** (0.200 g scale) was 0.15 M. Alkynes were added as benzene solutions. ^b The final ratio (by volume) of indicated solvent to benzene (from bromo alkyne solution) to THF or hexanes (from KHMDS or *n*-BuLi solutions) was 60:30:10. ^c Isolated yields of products purified by column chromatography. ^d Reaction at 75 °C. ^e Copper(I) thiophene-2-carboxylate. ^f Yield based on 1-bromo-2-phenylacetylene. ^g Yield improved to 76% when scale increased to 2.0 g of **255**. ^h 4.0 equiv of diamine ligand MeN(H)CH₂CH₂N(H)Me. ⁱ Reaction for 90 h.

¹³² No additional conversion of carbamate to ynamide was observed when extending the reaction time beyond 20 h.

The structural assignment for ynamide **256** was based on an analysis of IR and ^1H and ^{13}C NMR data. The IR spectrum shows a strong diagnostic carbon-carbon triple bond stretching band at 2245 cm^{-1} , which is consistent with data reported for a number of related ynamides.⁹⁰ In addition, the IR spectrum exhibits a carbonyl stretching band 1729 cm^{-1} . The ^1H NMR spectrum provides little diagnostic information for the alkyne itself; however, the methoxy group protons appear as a singlet at 3.84 ppm, the two methylenes appear as triplets at 3.11 and 3.88 ppm, and the aromatic region contains resonances integrating to ten protons. The ^{13}C NMR spectrum is more revealing: the two alkynyl carbons of the ynamide appear as characteristically broad resonances at 71.0 and 82.7 ppm. The rest of the ^{13}C NMR data is also in good agreement with resonances from previously reported ynamides.⁹⁰ The carbonyl carbon appears at 155.6 ppm, the carbon of the methoxy group appears at 54.1 ppm, the two methylenes appear at 34.2 and 51.4 ppm, and there are eight signals in the aromatic region between 123.2 and 138.0 ppm.

IR (neat): 3028, 2953, 2245, 1729, 1600, 1442, 1307 cm^{-1}

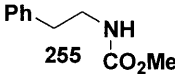
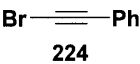
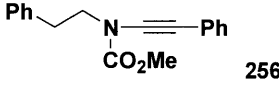
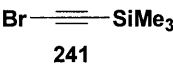
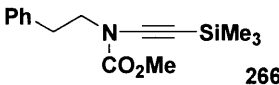
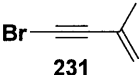
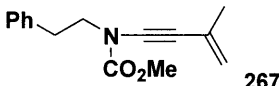
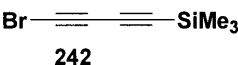
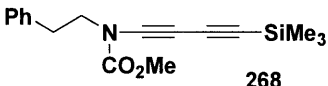
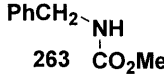
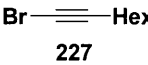
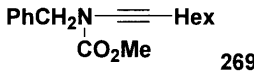
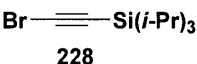
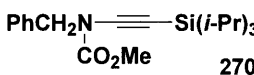

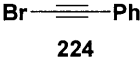
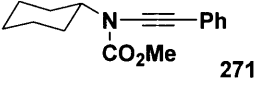
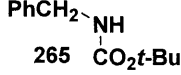
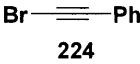
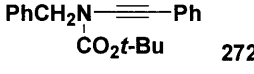
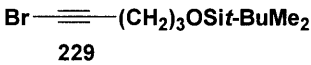
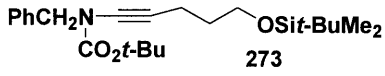
^{13}C NMR (125 MHz, CDCl_3):



^1H NMR (500 MHz, CDCl_3): 7.48 (d, $J = 6.7\text{ Hz}$, 2H), 7.28-7.39 (m, 8H), 3.88 (t, $J = 7.5\text{ Hz}$, 2H), 3.84 (s, 3H), 3.11 (t, $J = 7.5\text{ Hz}$, 2H)

Table 3 details the scope of the N-alkynylation reaction as applied to acyclic carbamates. Both methyl and *tert*-butyl carbamates are competent substrates for the reaction. A broad range of substituted and functionalized alkynyl bromides participate in the reaction, including systems we found to be especially prone to homocoupling such as the bromo derivatives of conjugated enynes (**231**) and arenynes (**224**). As a result, we were able to synthesize a variety of ynamides bearing aryl, alkenyl, alkyl, and silyl substituents on the acetylene. In addition, to the best of our knowledge, **268** appears to be the first known example of a diynamide, an interesting class of synthetic building blocks with considerable potential in organic synthesis.

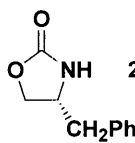
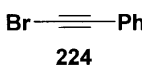
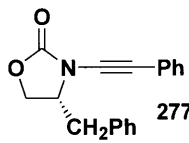
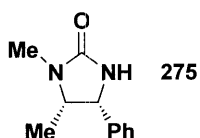

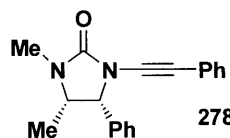
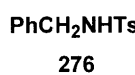
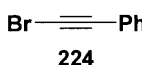
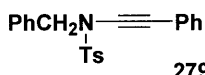
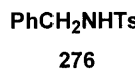
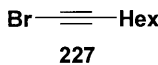
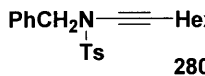
Table 3. Synthesis of Ynamides by N-Alkynylation of Acyclic Carbamates

$ \begin{array}{c} \text{R}^1\text{-N}^{\text{H}} \\ \text{CO}_2\text{R}^2 \end{array} \xrightarrow[\text{pyr}^a, \text{rt, 2 h}]{1.0 \text{ equiv KHMDS}, 1.0 \text{ equiv CuI}} \left[\begin{array}{c} \text{R}^1\text{-N}^{\text{CuL}_n} \\ \text{CO}_2\text{R}^2 \end{array} \right] \xrightarrow[\text{rt, 20 h}]{\text{then add } 2.0 \text{ equiv Br-C}\equiv\text{C-R}^3} \begin{array}{c} \text{R}^1 \\ \text{N} \equiv \text{C-R}^3 \\ \text{R}^2\text{O}_2\text{C} \end{array} $				
entry	carbamate	alkyne	ynamide	yield (%) ^b
1	 255	 224	 256	76
2	255	 241	 266	56
3	255	 231	 267	65
4	255	 242	 268	40
5	 263	 227	 269	50
6	263	 228	 270	74
7	 264	 224	 271	42
8	 265	 224	 272	61
9	265	 229	 273	53

^a KHMDS was added as a solution in THF and the alkynyl bromide was added as a solution in benzene. After all the reagents were added, the final ratio by volume of pyridine to benzene to THF was approximately 60:30:10. ^b Isolated yields of products purified by column chromatography.

As summarized in Table 4, we have also found that our alkylation protocol can be applied with good results to several other classes of amide derivatives. Oxazolidinones, imidazolidinones, and sulfonamides are successfully converted to ynamides, and it is noteworthy that our protocol is able to provide alkynyl sulfonamides such as **280** bearing alkyl substituents on the acetylene which cannot be prepared via alkynyl(phenyl)iodonium salts (*vide supra*).

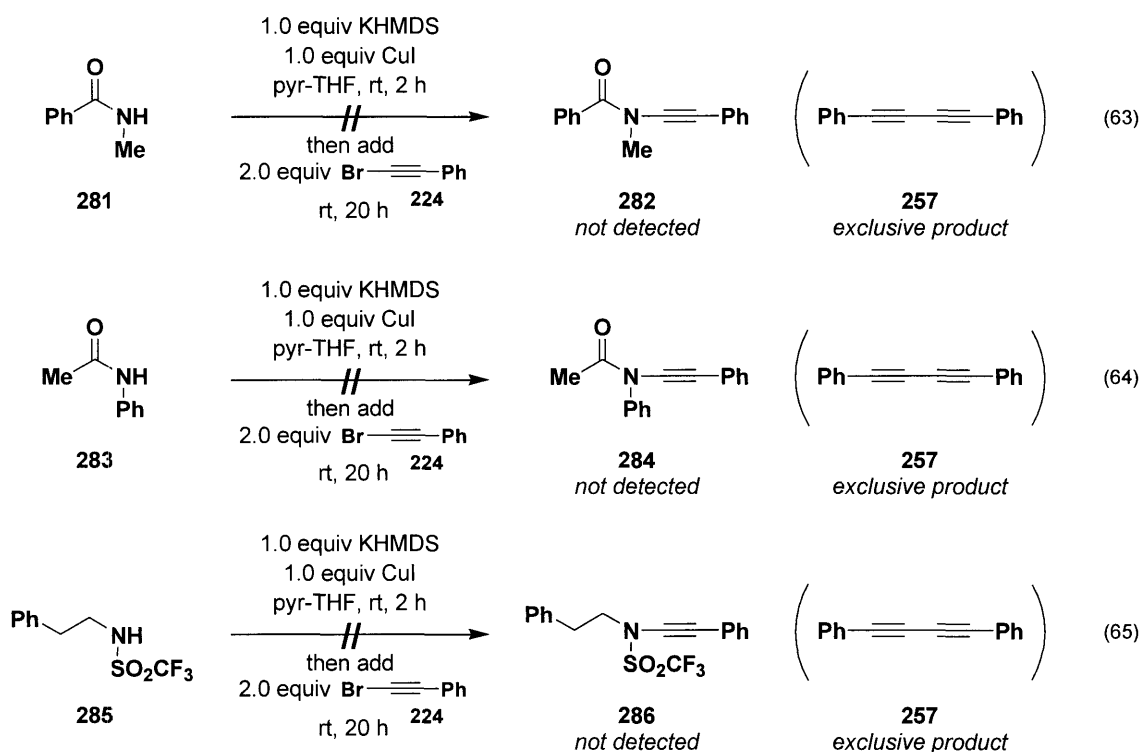
Table 4. N-Alkynylation of Sulfonamides and Cyclic Carbamates and Ureas

entry	carbamate	alkyne	ynamide	yield (%) ^b
1	 274	 224	 277	74
2	 275	 224	 278	60
3	 276	 224	 279	78
4	 276	 227	 280	42

^a Amide derivative was treated with 1.0 equiv each of KHMDs and CuI in pyridine-THF (rt, 2 h); 2.0 equiv of bromo alkyne in benzene was then added, and reaction mixture was stirred at rt for 20 h. The final ratio by volume of pyridine to benzene to THF was approximately 60:30:10. ^b Isolated yields of products purified by column chromatography.

In contrast to our success with carbamates, sulfonamides, and ureas, the application of our protocol to the N-alkynylation of carboxylic amides **281** and **283** did not furnish the expected ynamides, but rather led to diyne **257** as the exclusive product via homocoupling pathways (eq 63–64). These results are surprising, as Buchwald^{105c} and Porco¹¹⁰ both demonstrated that amides are successfully coupled to aryl and alkenyl halides using their copper-catalyzed procedures. In addition, Ogawa can synthesize enamides from the reaction of preformed copper acetamides and benzamides with (*E*)-1-bromo-2-phenylethene.¹²⁸ It is not obvious why carboxylic amides do not participate in our N-alkynylation reaction, although it is worth noting

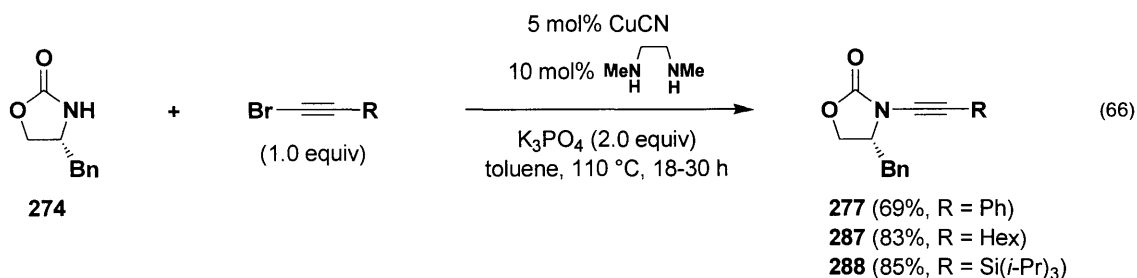
that Ph-C≡C-Br is much more susceptible to homocoupling than aryl and alkenyl bromides. In addition, the application of our protocol to the coupling of triflamide **285** with Ph-C≡C-Br failed to generate ynamide **286**. We were unable to find evidence in the literature, however, that triflamides participate in any type of transition-metal-catalyzed carbon-nitrogen bond-forming reactions.



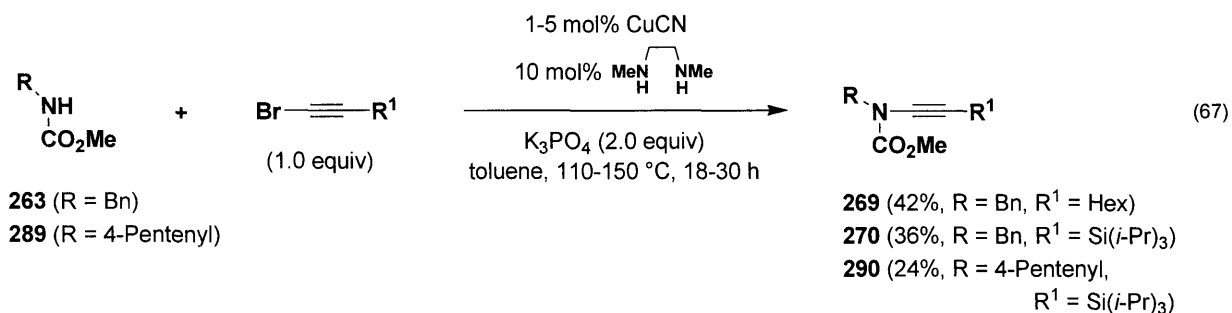
Subsequent Developments in Copper-Catalyzed N-Alkynylations

During the course of our studies, an important communication by Hsung and co-workers appeared reporting the successful application of Buchwald's copper catalyst system^{105c} to the N-alkynylation of oxazolidinones and lactams (eq 66).^{90,133} This procedure has the advantage of employing a catalytic amount of copper, but requires elevated temperatures in contrast to our room temperature conditions. Whereas our protocol employs an excess of bromo alkyne to compensate for homocoupling, interestingly Hsung reported that the yield of ynamides *decreases* when more than one equivalent of alkynyl halide is used under Buchwald conditions. Hsung

¹³³ For a subsequent report by Urabe and Sato using Buchwald's copper catalyst system for the coupling of sultams with alkynyl bromides, see ref 53c.

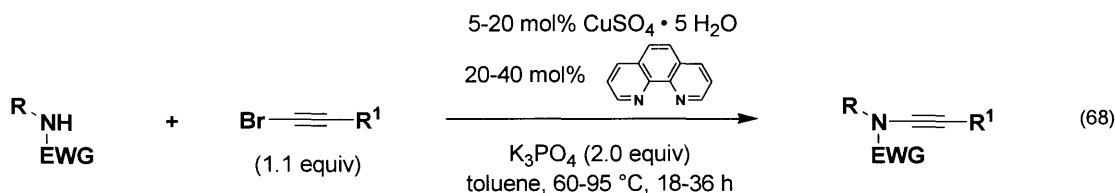


is able to convert oxazolidinone **274** to ynamide **277** in 69% yield using his procedure (eq 66), and our protocol provides this same ynamide in a comparable 74% yield (Table 4, entry 1). Hsung found his conditions, however, to be less effective when applied to other amide derivatives such as imidazolidinones, sulfonamides, and the *acyclic* carbamates that we are most interested in making for our cycloaddition studies. For example, Hsung reported a yield of 10% for the coupling of cyclic urea **275** (Table 4) and octynyl bromide, and he found that sulfonamides do not undergo N-alkynylation using his method. Somewhat better results were obtained in the case of acyclic carbamates; by terminating the reaction at 30–50% conversion, Hsung and co-workers were able to isolate the desired ynammides, albeit in low yield (eq 67). It is possible that Hsung observed incomplete conversion of acyclic carbamate due to the thermal decomposition of haloacetylenes at high temperatures. By comparison, our N-alkynylation protocol affords **269** in 50% yield and **270** in 74% yield (Table 3, entries 5–6).



Oxazolidinones and lactams appear to be favored substrates for copper-catalyzed alkynylation as reported by Hsung. Note that Hsung found that $\text{Ph}-\text{C}\equiv\text{C}-\text{Br}$ reacts with oxazolidinone **274** in 69% yield (eq 66), whereas we found that under these same Buchwald conditions the acyclic carbamate **255** furnished only traces of ynamide and mainly gave diyne from homocoupling in near quantitative yield (eq 58).

One year after his initial communication, Hsung reported a second-generation catalyst system for the coupling of amide derivatives with alkynyl halides.¹³⁴ In this new publication, Hsung confirmed that the previous CuCN-diamine system readily promoted the dimerization of certain alkynyl halides such as Ph-C≡C-Br, and he presented a new alkynylation protocol which addressed the limitations of the previous method. By replacing the CuCN-*N,N*-dimethylethylenediamine complex with CuSO₄-1,10-phenanthroline,¹³⁵ Hsung is able to suppress the dimerization of haloacetylenes and improve the yields of alkynylation for several classes of amide derivatives such as sulfonamides, imidazolidinones, and acyclic carbamates which previously did not participate efficiently in the coupling reaction (eq 68).



Although the second-generation catalyst system reported by Hsung is an important development that expanded the scope of haloacetylenes and amide derivatives for copper-catalyzed coupling, this CuSO₄-phenanthroline protocol still requires elevated temperatures and may be unsuitable for the preparation of thermally sensitive ynamides. Our method, by comparison, effects the N-alkynylation of amide derivatives at *room temperature*, and we therefore believed these mild conditions would generally be superior for the synthesis of our enyne cycloaddition substrates. In addition, our method provides ynamides within 20 h, whereas Hsung often requires significantly longer reaction times for good conversion of starting materials.

We were interested in comparing the efficiency of our protocol and Hsung's CuSO₄-phenanthroline protocol for the preparation of various ynamides (Table 5). After demonstrating that we could reproduce the results for ynamide **291** reported by Hsung using the CuSO₄-phenanthroline system (entry 1), we turned our attention to the synthesis of ynamides from acyclic carbamates using both our procedure (conditions A) and Hsung's improved second-

¹³⁴ Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, 6, 1151.

¹³⁵ For examples of 1,10-phenanthroline as a ligand in copper-catalyzed amidations of aryl halides, see: (a) Kiyomori, A.; Marcoux, J.-F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, 40, 2657. (b) Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, 3, 3803. (c) Evindar, G.; Batey, R. A. *Org. Lett.* **2003**, 5, 133. Also see refs 106b-c.

generation procedure (conditions **B**). As shown in the table, both protocols couple methyl carbamates with conjugated bromo arenynes and enynes in comparable yield that reflect a similar degree of conversion of amide starting material (entries 1 and 3). Our method is more efficient for reactions involving octynyl bromide (entry 2) and the allyl substituted alkynyl bromide (entry 4), although it is interesting to observe that the yield for alkynylation of the latter bromide under Hsung's conditions improved considerably when switching from *N*-allyl to *N*-benzyl carbamate (compare entries 4–5). Finally, we observed that our method is particularly well-suited for the preparation of diynamides such as **296**¹³¹ (entry 6).

Table 5. Comparison of N-Alkynylation Protocols

entry	ynamide	conditions (yield)	entry	ynamide	conditions (yield)
1		291 A (62%) B (74%, 73% ^a)	4		294 A (39%) B (<5% ^b)
2		292 A (60%) B (44%, 47% ^b)	5		295 B (34% ^b)
3		293 A (67%) B (65%)	6		296 A (66% ^c) B (36%, 18% ^d)

A: 1.0 equiv carbamate, KHMDS, CuI, pyr-THF, rt, 2 h; then add 2.0 equiv alkyne (in benzene solution), rt, 20 h

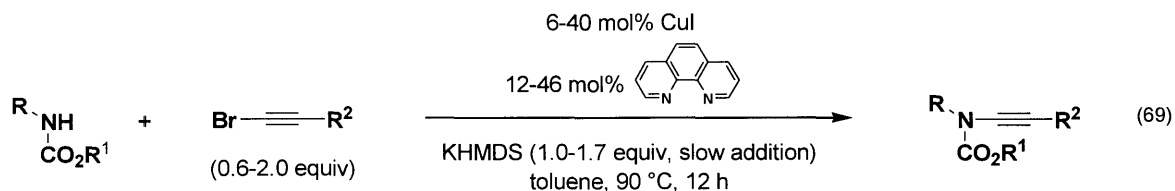
B: 1.0 equiv carbamate, 1.1 equiv alkyne, 0.20 equiv CuSO₄·5 H₂O, 0.40 equiv 1,10-phen, toluene or benzene, 65 °C, 30–40 h

^a Yield reported by Hsung (ref 134). ^b Reaction at 95 °C. ^c Reaction with 1.2 equiv alkyne. ^d Reaction with 1.0 equiv CuSO₄·5 H₂O, 2.0 equiv 1,10-phenanthroline.

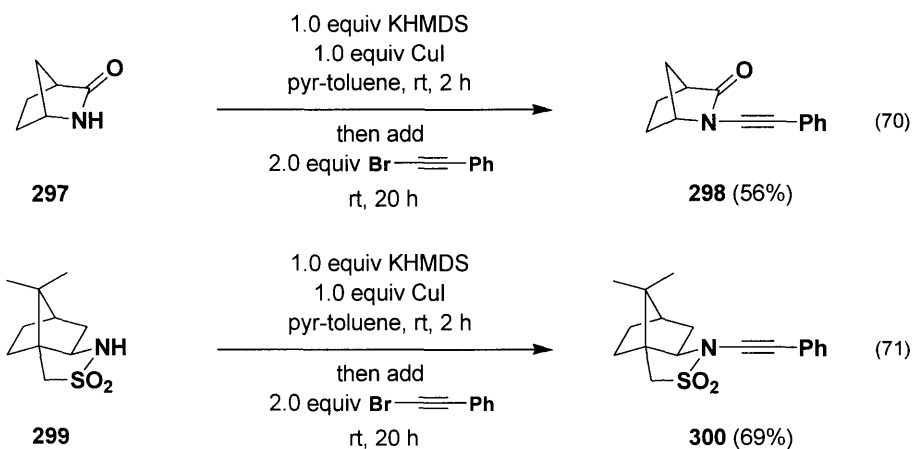
During the course of writing this thesis, a report appeared in the literature by Tam which offered another procedure for the copper-catalyzed alkynylation of acyclic carbamates.¹³⁶ This new method combines aspects of our protocol and the Hsung second-generation protocol by using catalytic CuI and 1,10-phenanthroline in toluene at elevated temperatures with the slow addition of a strong base (KHMDS) to the reaction mixture (eq 69). Slow addition of KHMDS was found to be necessary to avoid the formation of unreactive diamido cuprates from excess deprotonated carbamate and catalytic copper salts.^{105c} Preliminary investigations conducted group member Lucy Kohnen¹³¹ have not shown any benefit to replacing our original alkynylation procedure with the protocol of Tam, as the latter method requires heating, the slow

¹³⁶ Riddell, N.; Villeneuve, K.; Tam, W. *Org. Lett.* **2005**, 7, 3681.

addition of KHMDS over a period of several hours (which may be inconvenient), and thus far appears to effect N-alkynylations in lower yield than our protocol.



Tam and co-workers also applied our original alkylation protocol for the synthesis of ynamides required for their study. Tam effected the coupling of lactam **297** and sultam **299** with Ph-C≡C-Br using our procedure with the modification of administering KHMDS as a solution in toluene rather than THF (eq 70–71). Although we never applied our protocol to the alkylation of lactams, our attempts to couple acyclic amides to Ph-C≡C-Br led to homocoupling of the haloacetylene (eq 63–64). Curiously, however, Tam reports being unable to reproduce our successful coupling of Ph-C≡C-Br with carbamate **264** (Table 3, entry 7)¹²⁹ and carbamate **263** (Table 5, entry 1).^{131,137} We are currently investigating the reasons that might have contributed to Tam's inability to apply our method to the alkylation of carbamates.¹³¹ One possible explanation is that Tam's reactions may be compromised by the use of wet pyridine, as we have found that employing freshly distilled pyridine is essential for obtaining reproducible results.



¹³⁷ Tam also is unable to effect these couplings with the copper-catalyzed protocols developed by Hsung.

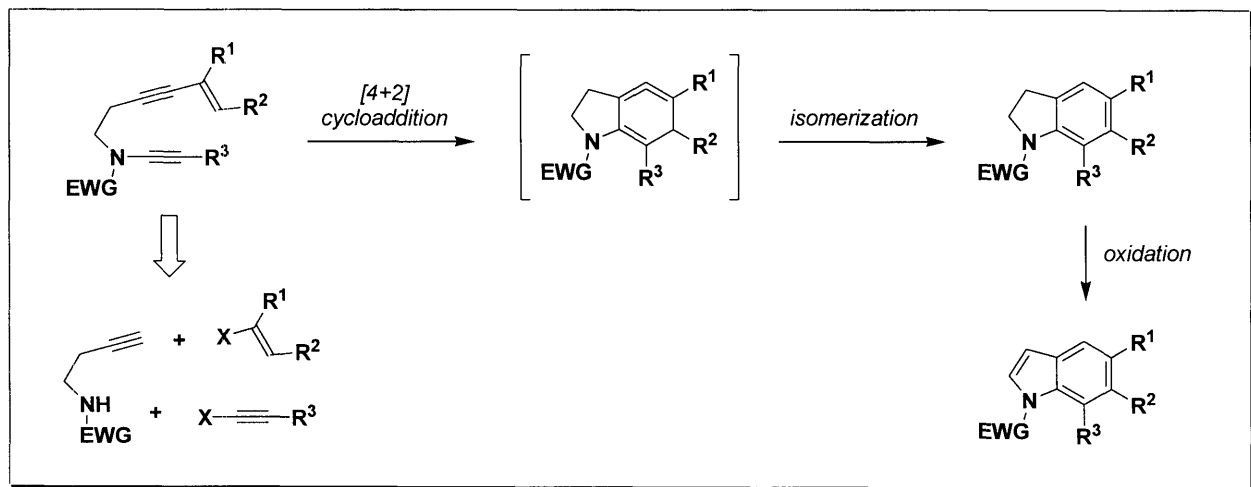
Summary

We designed and developed a strategy for the synthesis of ynamides via N-alkynylation of carbamates, ureas, and sulfonamides. Our protocol forms copper amide derivatives before exposure to alkynyl halides to compensate for competitive homocoupling pathways which consume the haloacetylene. The coupling of amide derivatives with various alkynyl halides allows for the synthesis of ynamides with diverse substitution on the acetylene. These alkynylations proceed efficiently at room temperature and provide us with a method for the preparation of our thermally sensitive cycloaddition substrates under mild conditions.

Chapter 5

Synthesis of Indolines and Indoles via Intramolecular [4 + 2] Cycloadditions of Ynamides and Conjugated Enynes

The strategy we envisioned for the synthesis of highly substituted indolines and indoles involved the intramolecular [4 + 2] cycloaddition of ynamides with conjugated enynes.¹³⁸ As discussed in Chapter 1 (see page 17), we anticipated that conjugated enynes and ynamides would combine in a [4 + 2] cycloaddition to form a highly strained isoaromatic cyclic allene intermediate as shown below. Isomerization of the cyclic allene via bimolecular proton or hydrogen atom transfer pathways would then provide indolines which are highly substituted on the six-membered ring. Finally, if desired, oxidation of the indolines would afford indoles. We believed that an especially attractive feature of this divergent strategy would be the convenient accessibility of cycloaddition substrates from simple derivatives of 3-butyneamine. Sonogashira coupling of homopropargyl amide derivatives would assemble the enyne moiety and subsequent N-alkynylation using the chemistry described in Chapter 4 would install the ynamide. We anticipated that this highly modular approach would be particularly well-suited for the preparation of libraries of substituted indolines and indoles.

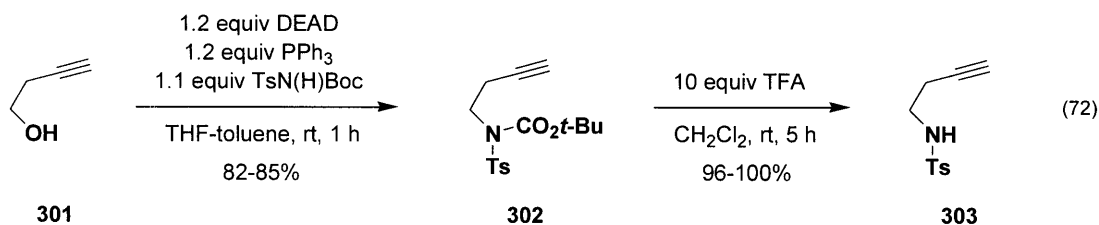


¹³⁸ The work presented in this chapter has appeared in a communication: Dunetz, J. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 5776.

Preparation of Substrates for Cycloaddition Studies

We began our investigation of the cycloadditions of conjugated enynes with ynamides before developing our protocol discussed in the previous chapter for the copper-mediated coupling of amide derivatives and alkynyl halides. Originally we planned to synthesize ynamides using alkynyl(phenyl)iodonium methodology (Chapter 3), and thus our early cycloaddition substrates were constructed from sulfonamides since this class of amide derivatives were known to participate in N-alkynylation reactions with iodonium salts. Although the reaction of amines with sulfonyl chlorides provides a straightforward route to sulfonamides, neither 3-butynylamine nor its ammonium salt were commercially available when we began our studies. As a result, it was necessary to explore other synthetic approaches to the homopropargyl sulfonamides which would serve as linchpins for the divergent syntheses of our initial cycloaddition substrates.

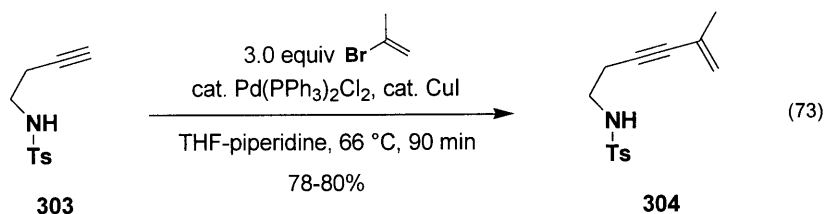
Our approach to the synthesis of sulfonamides such as **303** involved the Mitsunobu reaction of 3-butyn-1-ol (**301**) using protected nitrogen nucleophiles such as TsN(H)Boc according to the method of Weinreb.¹³⁹ We generated TsN(H)Boc in quantitative yield from the slow addition of tosyl isocyanate to *tert*-butanol as described by Weinreb,¹³⁹ and then employed it in a Mitsunobu reaction with 3-butyn-1-ol (**301**) as shown in eq 72 to afford **302** in good yield. Treatment of **302** with trifluoroacetic acid cleaved the carbamate and liberated **303** in near quantitative yield.



As previously mentioned, we envisioned constructing our cycloaddition substrates via successive coupling reactions involving first the alkyne and then the nitrogen atom of homopropargyl amine derivatives such as **303**. Sonogashira coupling reactions are powerful methods for converting terminal alkynes to conjugated enynes by reaction with various alkenyl

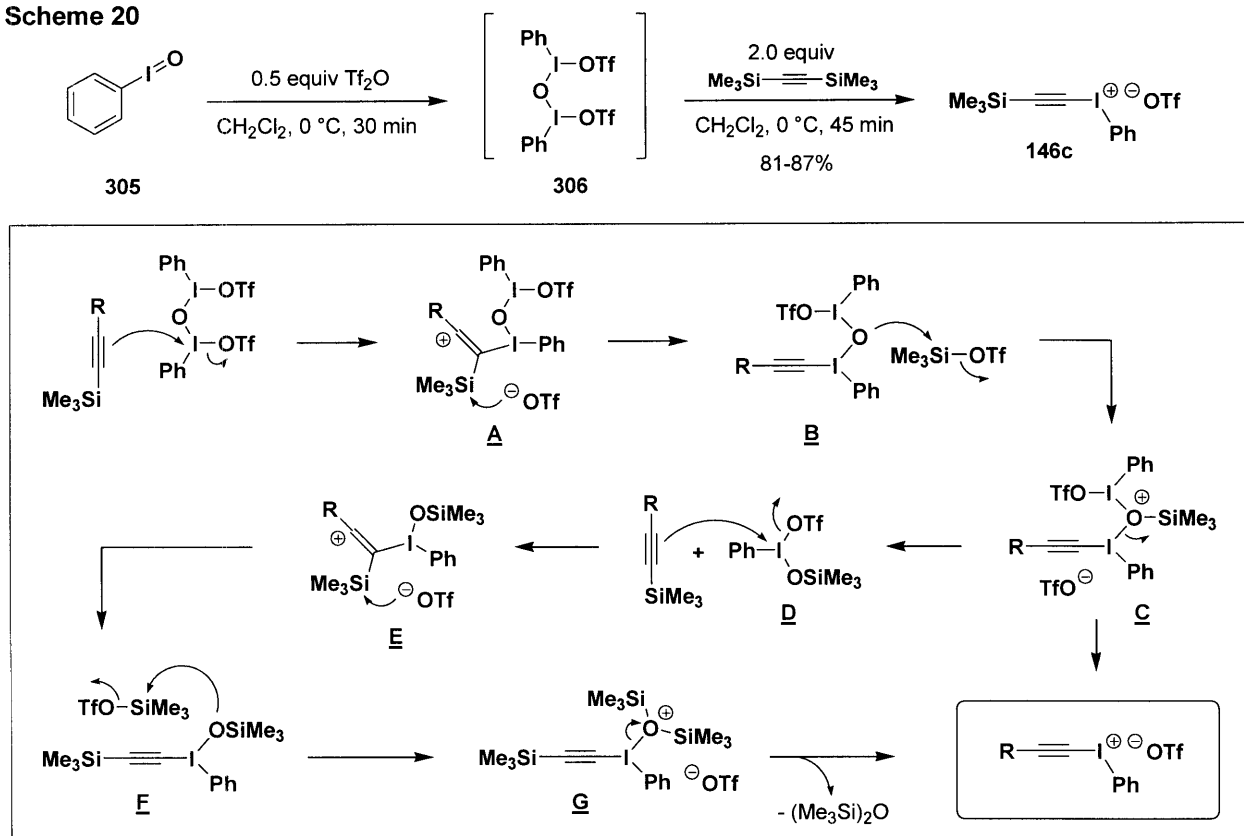
¹³⁹ Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, D., Jr.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709.

halide and sulfonate coupling partners.¹⁴⁰ We employed a catalyst system of $(\text{PPh}_3)_2\text{PdCl}_2$ and CuI in THF-piperidine to couple alkynes with commercially available 2-bromopropene for the synthesis of enynes such as **304** which bear a methyl substituent.



The alkynyl(phenyl)iodonium salts required for the N-alkynylation of our sulfonamides such as **304** were prepared according to the procedure of Stang^{75c} via the reaction of alkynylsilanes with Zefirov's reagent **306**,¹⁴¹ which was generated in situ from iodosobenzene.

Scheme 20

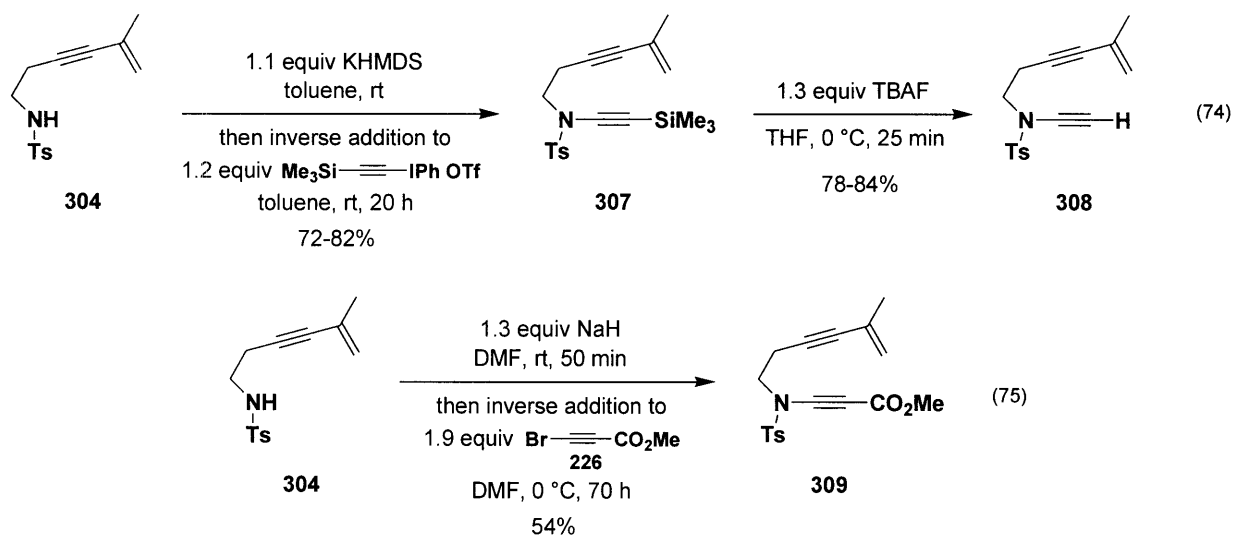


¹⁴⁰ For a review of the Sonogashira reaction, see: Sonogashira, K. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i.; de Meijere, A.; Eds.; Wiley-Interscience: New York, 2002; Vol. 1, pp 493–529.

¹⁴¹ (a) Zefirov, N. S.; Zhdankin, V. V.; Dan'kov, Y. V.; Koz'min, A. S. *J. Org. Chem. USSR (Engl. Transl.)* **1984**, 20, 401. (b) Gallos, J.; Varvoglis, A.; Alcock, N. W. *J. Chem. Soc., Perkin Trans. 1* **1985**, 757.

The mechanism of this iodonium salt formation is shown in Scheme 20 and involves the electrophilic addition of Zefirov's reagent to an alkynylsilane to generate an equivalent of the desired alkynyl(phenyl)iodonium salt and another iodine(III) reagent (**D**). Electrophilic addition of **D** to a second alkynylsilane then produces another equivalent of iodonium salt.

Equation 74 outlines the N-alkynylation of sulfonamide **304**. Deprotonation of **304** and addition of the potassium salt to the alkynyl(phenyl)iodonium salt **146c** generated silyl ynamide **307** in good yield. Desilylation then provided terminal ynamide **308** which we originally anticipated would serve as an entry point to more functionalized ynamides via alkylation or acylation of the acetylene.¹⁴² Sulfonamide **304** also served as a precursor to the “push-pull” ynamide **309**, which we prepared using the protocol developed by former group member Brenda Palucki for the addition of sodium sulfonamides to methyl 3-bromopropiolate.^{33c}

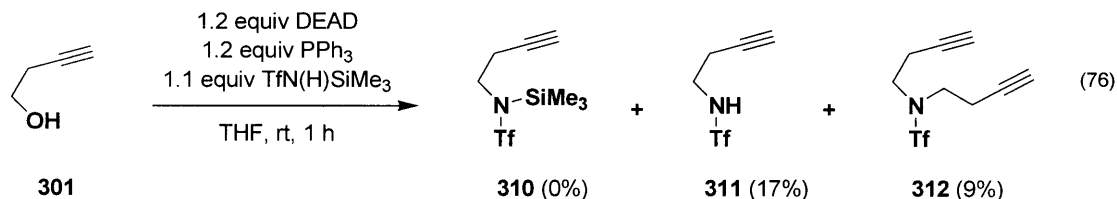


We also were interested in preparing compounds with different electron-withdrawing groups on the nitrogen atom in order to compare the cycloadditions of electronically diverse ynamides, and so we next applied our Mitsunobu strategy to the synthesis of the homopropargylic triflamide **311**. TfN(H)SiMe₃¹⁴³ was prepared as a potential nucleophile for Mitsunobu reaction with 3-butyne-1-ol, and we envisioned that the labile silyl protective group would be easily cleaved from the Mitsunobu product **310** in a subsequent step. The trimethylsilyl group, however, proved not to be stable to our Mitsunobu conditions, and although

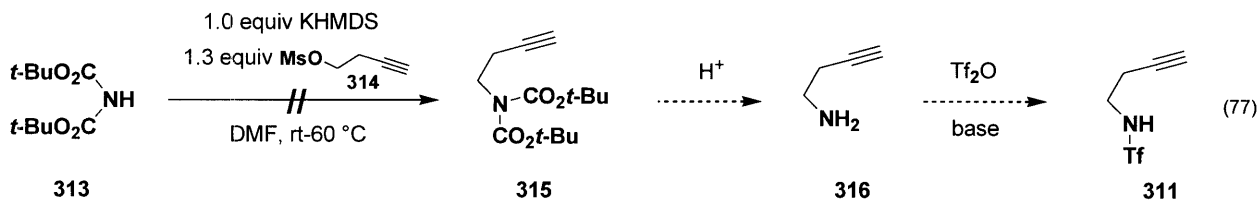
¹⁴² We later abandoned this linear approach to substituted ynamides in favor of our strategy for copper-mediated couplings of amide derivatives with alkynyl halides.

¹⁴³ Roy, A. K. *J. Am. Chem. Soc.* **1993**, *115*, 2598.

we were able to obtain triflamide **311** (albeit in poor yield) without a separate deprotection step, the further reaction of **311** with alcohol **301** led to the dialkyl triflamide **312** as a side product.



As mentioned earlier, the most direct route to compounds such as triflamide **311** involves the direct sulfonylation of 3-butynylamine (**316**). Since our Mitsunobu strategy failed to provide **311** in good yield, we turned our attention instead to the preparation of **316**. Our approach to the homopropargyl amine involved a modified Gabriel synthesis^{144,145} in which mesylate **314**¹⁴⁶ would alkylate the potassium salt of di-*t*-butyl iminodibutylcarbamate.¹⁴⁷ Attempts to effect this alkylation were unsuccessful, however, presumably due to decomposition of mesylate **314** to vinylacetylene via elimination under the basic reaction conditions.



Our difficulties preparing homopropargyl triflamide **311** led us to pursue an alternative route to *N*-triflyl cycloaddition substrates. Our revised strategy involved the ring opening of an aziridine with an alkynylmetal reagent (eq 78). Whereas the literature contained scattered reports of the addition of metalated acetylides to *N*-tosyl aziridines,¹⁴⁸ the analogous reaction

¹⁴⁴ For a review, see: Mitsunobu, O. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Oxford: Pergamon, 1991; Vol. 6, pp 79–83.

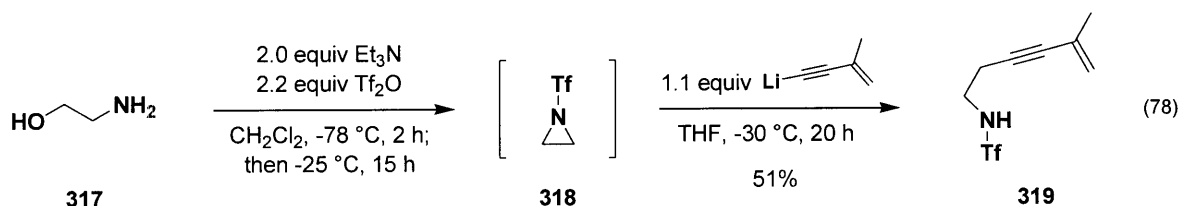
¹⁴⁵ For other preparations of 3-butynylamine (**316**) via modified Gabriel synthesis, see: (a) Bestmann, H. J.; Wölfel, G. *Angew. Chem. Int. Ed.* **1984**, 23, 53. (b) Qiao, C.; Jeon, H.-B.; Sayre, L. M. *J. Am. Chem. Soc.* **2004**, 126, 8038.

¹⁴⁶ Mesylate **314** was prepared in 99% yield from alcohol **301** with 1.3 equiv MsCl and 1.8 equiv Et₃N in THF.

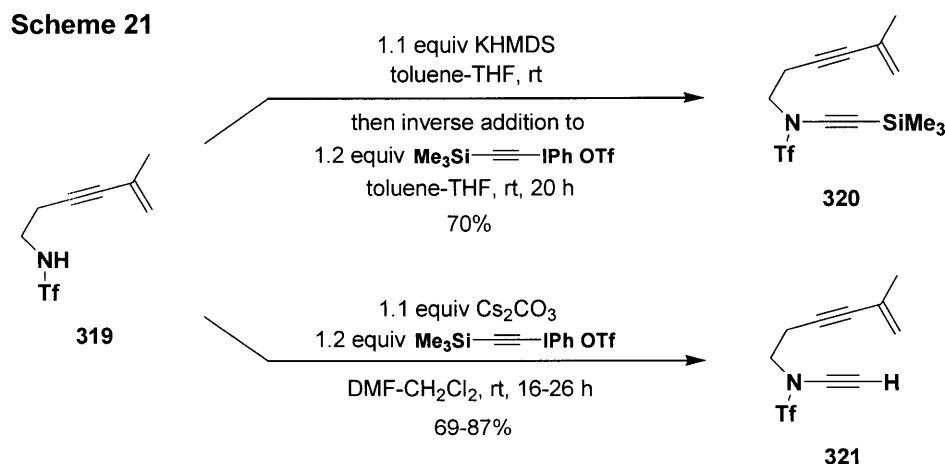
¹⁴⁷ For the preparation of **313** as a versatile Gabriel reagent, see: Grehn, L.; Ragnarsson, U. *Synthesis* **1987**, 275.

¹⁴⁸ For examples, see: (a) Compain, P.; Goré, J.; Vatele, J.-M. *Tetrahedron* **1996**, 52, 10405. (b) Fuji, K.; Kawabata, T.; Kiryu, Y.; Sugiura, Y. *Heterocycles* **1996**, 42, 701. (c) Church, N. J.; Young, D. W. *J. Chem. Soc., Perkin Trans. I*, **1998**, 1475. (d) Gronquist, M. R.; Meinwald, J. *J. Org. Chem.* **2001**, 66, 1075. (e) Turner, J. J.; Leeuwenburgh, M. A.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **2001**, 42, 8713. (f) Ding, C.-H.; Dai, L.-X.; Hou, X.-L. *Synlett* **2004**, 1691. Also see ref 57b.

with *N*-triflyl aziridines was unprecedented. We applied the general method of Moberg¹⁴⁹ to prepare the previously unknown parent *N*-triflyl aziridine **318** beginning from 2-aminoethanol. Aziridine **318** was prone to polymerization in the absence of solvent, and so we isolated the compound as a solution in THF for the subsequent reaction (see Experimental Section for details). Opening of the aziridine ring with lithium isopropenylacetylide then provided homopropargyl triflamide **319** containing the desired complete enyne moiety.



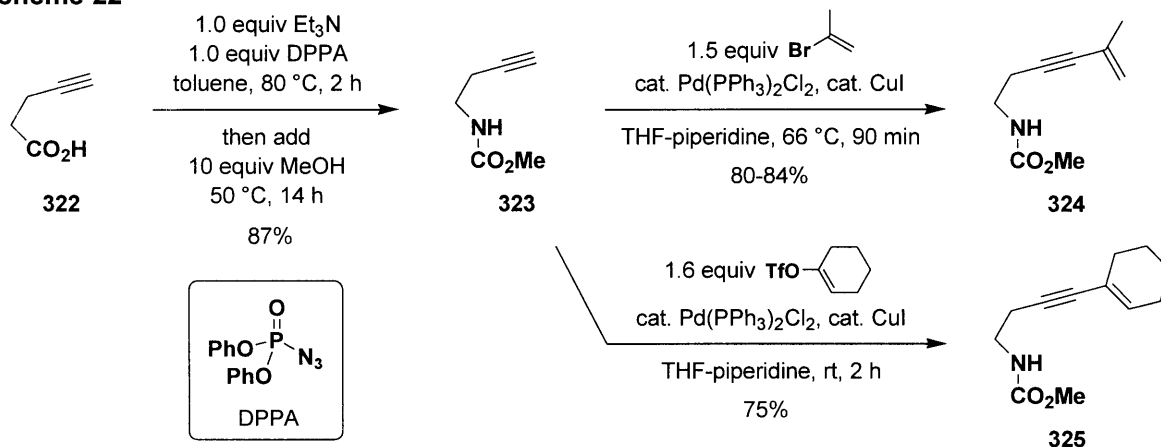
Alkynylation of **319** using the previously described alkynyl(phenyl)iodonium methodology provided several *N*-triflyl ynamides for our cycloaddition studies (Scheme 21). Deprotonation of the triflamide with KHMDS and addition of the resulting potassium derivative to the iodonium salt under anhydrous conditions afforded silyl ynamide **320**. It is interesting that the reaction of this triflamide with the same iodonium salt in the presence of cesium carbonate and DMF resulted in cleavage of the alkynylsilane and afforded **321** as the exclusive ynamide product. It is likely that trace amounts of water in the Cs_2CO_3 or DMF are promoting desilylation in this reaction.



¹⁴⁹ (a) Cernerud, M.; Adolfsson, H.; Moberg, C. *Tetrahedron: Asymmetry* **1997**, 8, 2655. (b) Cernerud, M.; Skrinning, A.; Bérègère, I.; Moberg, C. *Tetrahedron: Asymmetry* **1997**, 8, 3437.

We were pleased to have synthesized several *N*-sulfonyl ynamides for our cycloaddition studies, but we were also interested in building compounds with a weaker electron-withdrawing group on the nitrogen for several reasons. First, we were interested in examining the degree to which the rate and efficiency of cycloaddition are influenced by the electron character of the ynamide component. In addition, the oxidation of indolines to indoles occurs with greater facility when the lone pair of the nitrogen atom is more available to assist oxidative pathways (*vide infra*). We therefore next turned our attention to the synthesis of ynamides in which the nitrogen atom is protected as a carbamate rather than a sulfonamide derivative. Our plan for the synthesis of cycloaddition substrates of this type involved the application of homopropargyl carbamate **323** as a key synthetic linchpin. We prepared **323** from commercially available 4-pentynoic acid (**322**) using a modified Curtius rearrangement protocol involving diphenylphosphoryl azide (DPPA),¹⁵⁰ and our optimized conditions for this transformation are shown below. Sonogashira coupling of **323** with an alkenyl bromide or triflate then assembled the enyne components of **324** and **325**.

Scheme 22

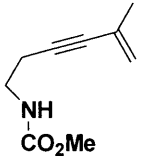
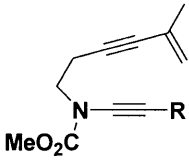


The application of our method for coupling amide derivatives with alkynyl halides provided the series of ynamides in Table 6. The alkynylation of carbamate **324** with various haloacetylenes provided ynamides with various silyl, alkyl, and aryl substituents on the acetylene.¹⁵¹ As discussed in the previous chapter, the yields for these reactions reflect the

¹⁵⁰ For a review of the Curtius rearrangement, see: (a) Smith, P. A. S. *Org. React.* **1946**, 337. For the modified Curtius reaction with DPPA, see: (b) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, 30, 2151.

¹⁵¹ Reaction of the potassium salt of **324** with alkynyl(phenyl)iodonium salt **146c** produced silyl ynamide **326** in poor yield with complete decomposition of the iodonium triflate.

Table 6. Preparation of Ynamide Cycloaddition Substrates

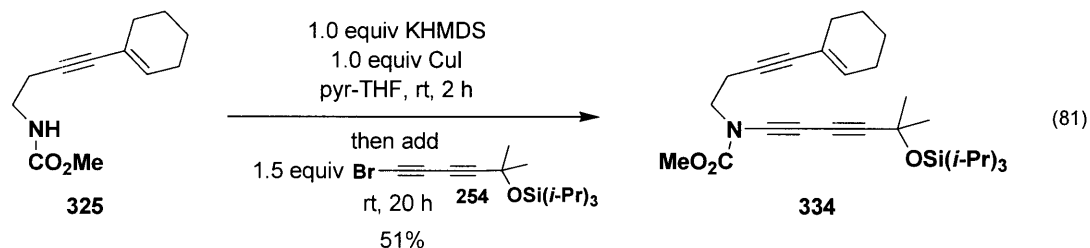
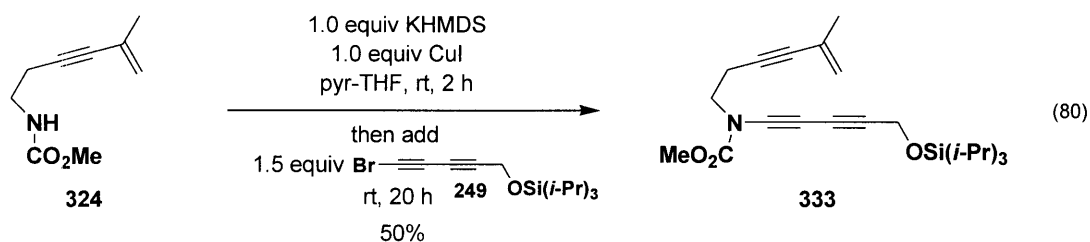
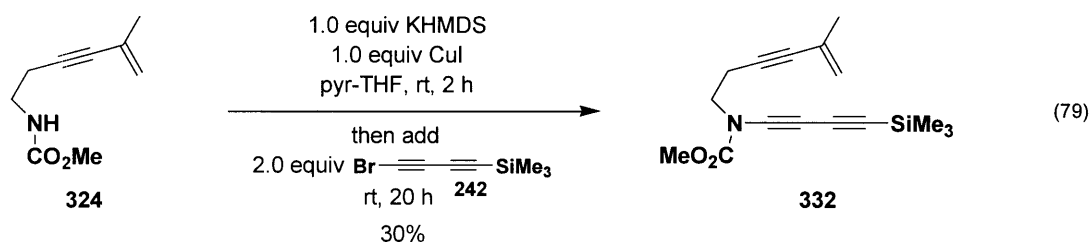
<div style="display: flex; align-items: center; justify-content: center;"> <div style="text-align: center;">  <p>324</p> </div> <div style="margin: 0 20px; text-align: center;"> <p>1.0 equiv KHMDS 1.0 equiv CuI pyr-THF, rt, 2 h</p> <hr style="width: 50%; margin: 0 auto;"/> <p>then add 2.0 equiv Br—C≡C—R rt, 20 h</p> </div> <div style="text-align: center;">  <p>326-331</p> </div> </div>			
entry	alkyne	ynamide	yield (%)
1	Br—C≡C—SiMe ₃ 241	326 (R = SiMe ₃)	56-59
2	Br—C≡C—Si(<i>i</i> -Pr) ₃ 228	327 (R = Si(<i>i</i> -Pr) ₃)	61-64
3	Br—C≡C—Ph 224	328 (R = Ph)	62
4	Br—C≡C—Hex 227	329 (R = Hex)	51
5	Br—C≡C—(CH ₂) ₃ OSi ^t -BuMe ₂ 229	330 (R = (CH ₂) ₃ OSi ^t -BuMe ₂)	40
6	Br—C≡C—CH ₂ OMe 225	331 (R = CH ₂ OMe)	39

degree of conversion of carbamate to ynamide, and the yields are nearly quantitative when corrected for recovered carbamate.¹⁵²

As discussed in Chapter 2, previous work in our laboratory has demonstrated that enyne cycloadditions are particularly facile when the 2π component is activated through conjugation to a second acetylenic unit. We therefore were interested in examining the utility of *diynamides* for our cycloaddition and prepared substrates **332–334**. The coupling of **324** with 1-bromo-4-(trimethylsilyl)butadiyne was sluggish and only provided the desired diynamide **332** in 30% yield (eq 79). Whereas we typically employ two equivalents of alkynyl halide in these reactions to compensate for decomposition via homocoupling pathways, we discovered that reactions with bromo diynes are more efficient with smaller excesses of haloacetylene (eq 80–81). Copper has a strong affinity for alkynes and we speculate that the excess bromo diyne coordinates to the

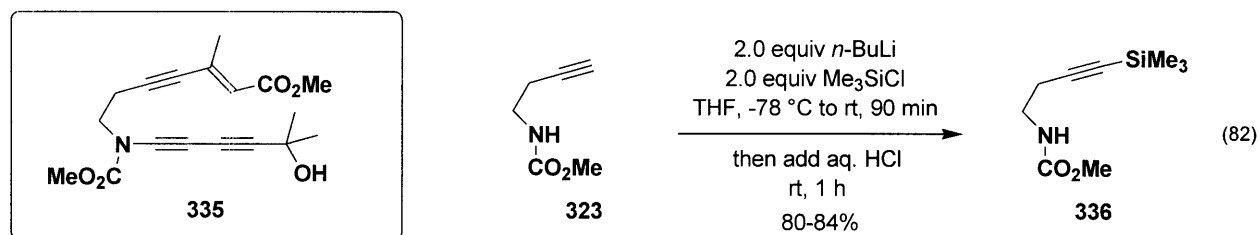
¹⁵² Yields for N-alkynylation did not improve with reaction times beyond 20 h.

metal in an overwhelming fashion which impedes the desired amidation pathway. Additional evidence suggests that excessive π -coordination may suppress the activity of copper in the N-alkynylation reaction. We previously reported that the coupling was sluggish when a large excess (5 equiv) of $\text{Ph-C}\equiv\text{C-Br}$ was employed (Table 2, entry 12).¹²⁹ In addition, Hsung has also found that the conversion of oxazolidinones to ynamides decreases dramatically when more than 1 equiv of haloacetylene is used for copper-catalyzed amidations under his conditions.⁹⁰

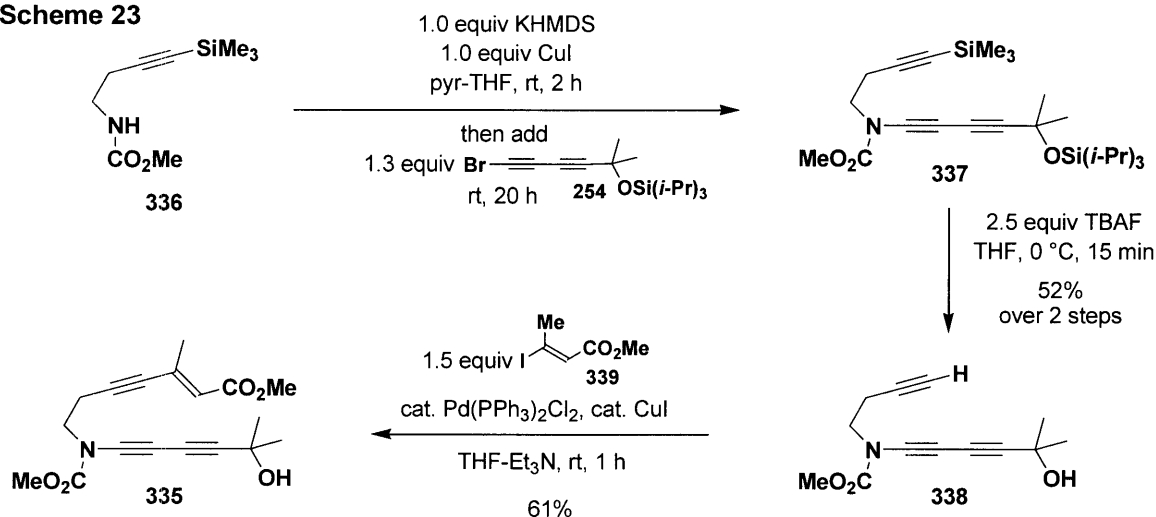


Another diynamide we were interested in studying is the cycloaddition substrate **335** in which the enyne bears an electron-withdrawing group. In this case, our approach involved ynamide formation before elaboration of the alkyne via Sonogashira coupling. We chose this synthetic strategy to avoid potential complications from the reaction of a copper amide derivative with the enyne Michael acceptor.

First, it was necessary to protect the acetylene of **323**, which was accomplished via bis-silylation of the alkyne and carbamate followed by protodesilylation of the silylamine. Alkynylation of the resulting carbamate **336** with a slight excess of bromo diyne provided diynamide **337** and global desilylation of both alkyne and alcohol provided **338**. Initial attempts

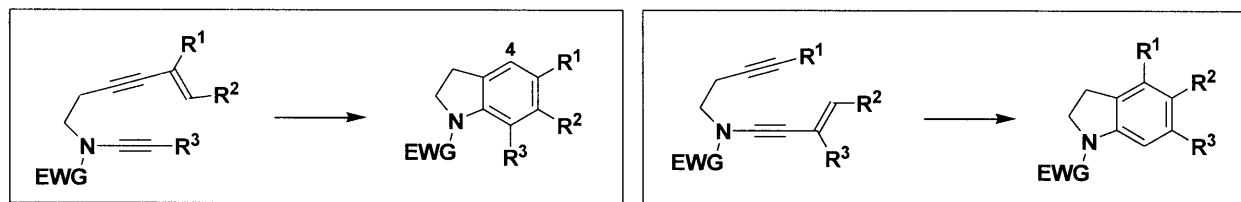


Scheme 23



to generate **335** via Trost's method for the alkynylpalladation of Michael acceptors such as methyl 2-butynoate were unsuccessful,¹⁵³ but we were able to access the enyne after Sonogashira coupling of the alkyne with iodide **339**.¹⁵⁴

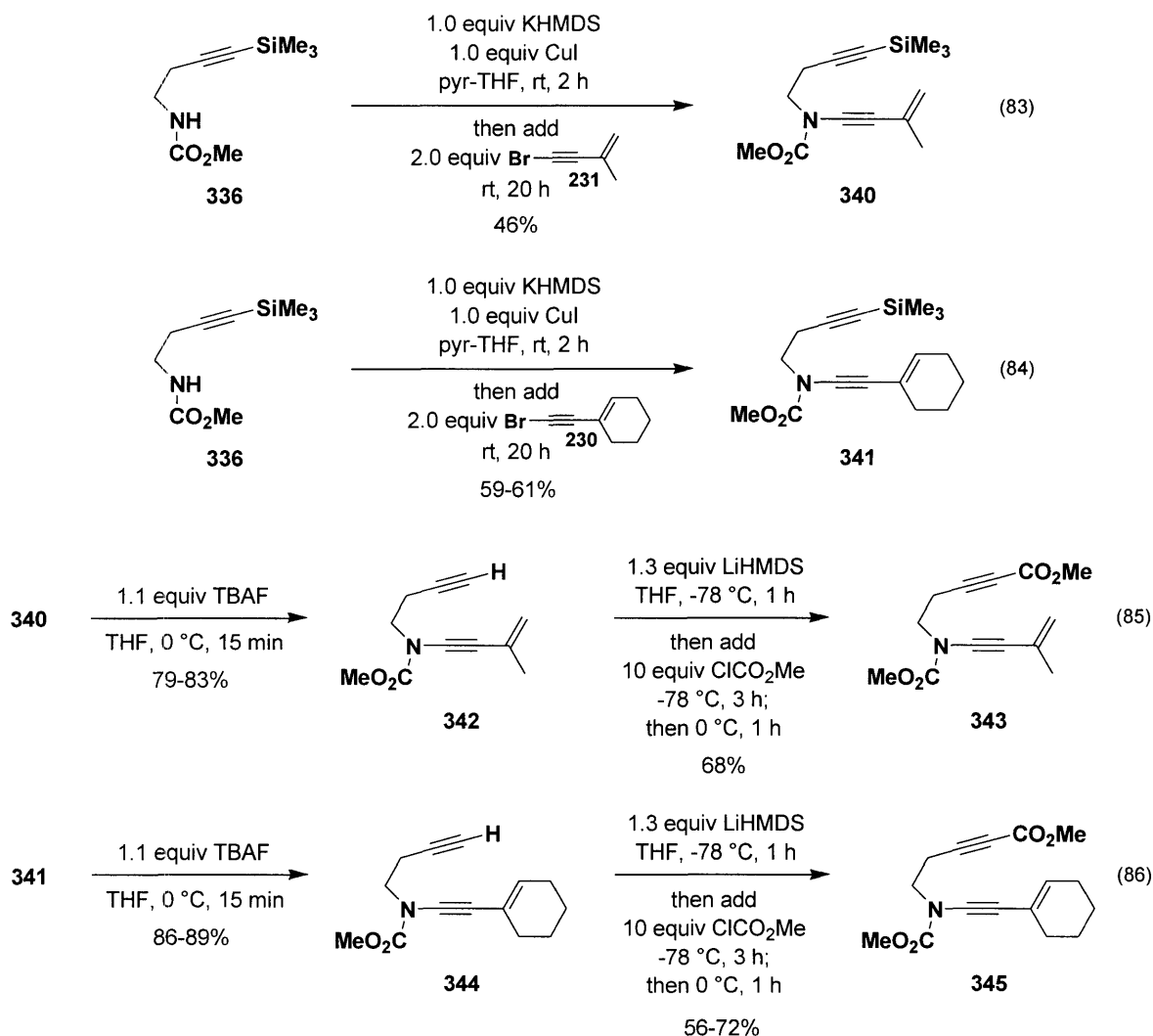
One significant limitation of the cycloaddition of conjugated enynes with ynamides is that the indoline products necessarily bear a hydrogen at the C-4 position (see below). We envisioned that access to indolines substituted at this site could be gained, however, via the cycloaddition of conjugated enynamides with tethered acetylenes. These complementary reactions would provide indolines and indoles with regiocontrolled access to substitution throughout the six-membered ring.



¹⁵³ Trost, B. M.; Sorum, M. T.; Chan, C.; Harms, A. E.; Rühler, G. *J. Am. Chem. Soc.* **1997**, *119*, 698.

¹⁵⁴ A procedure for the synthesis of iodide **339** was previously developed in our laboratory for the synthesis of (-)-ascochlorin. See: Dudley, G. B.; Takaki, K. S.; Cha, D. D.; Danheiser, R. L. *Org. Lett.* **2000**, *2*, 3407.

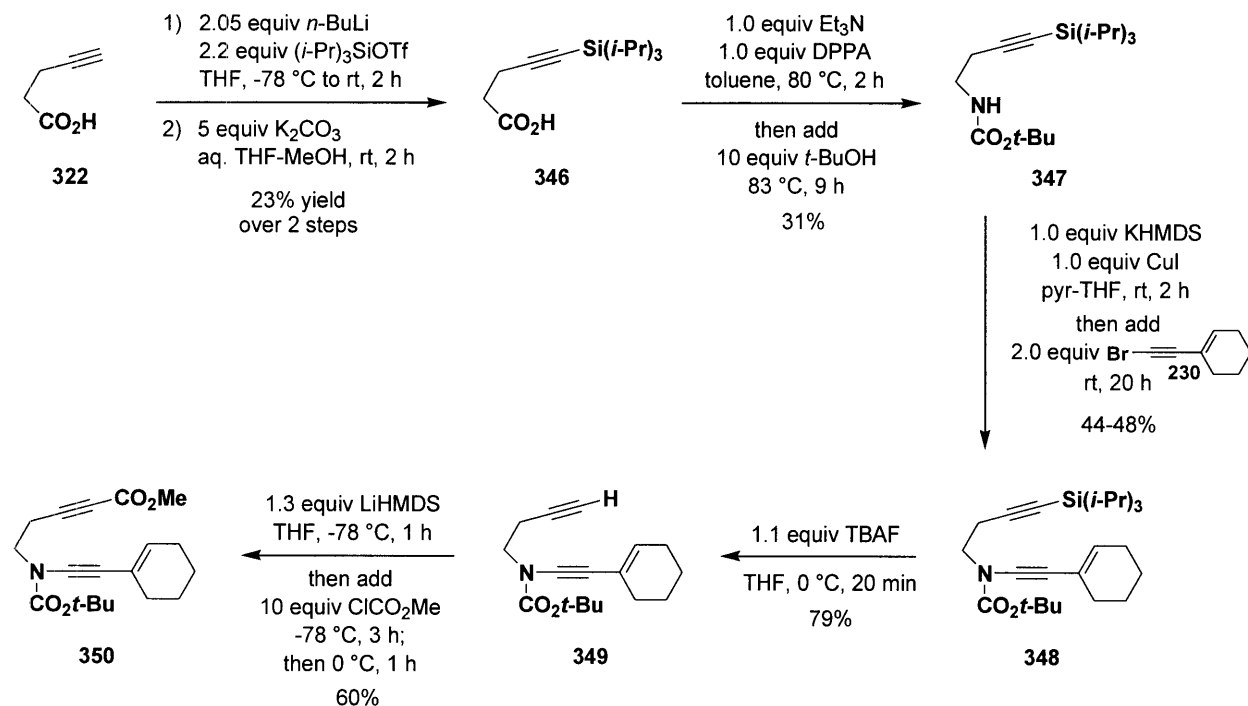
As shown in eq 83–84, we found that enynamides are available directly from the coupling of carbamate derivatives with bromo enynes such as **231** and **230**. After installation of the enynamide, desilylation of the 2π component and subsequent ester formation provided the desired cycloaddition substrates (eq 85–86). Several attempts to deprotonate **342** and **344** with other bases (e.g., *n*-BuLi, *i*-PrMgCl, KHMDS) led to rapid decomposition, but the optimized conditions shown below employing LiHMDS as the base provided the desired alkynyl esters **343** and **345** in good yields.



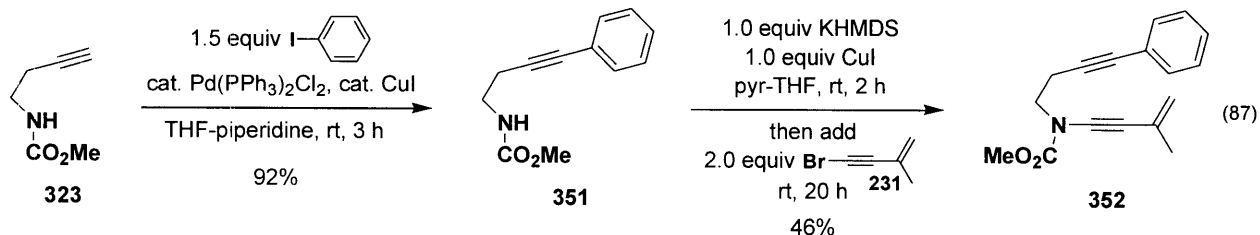
Another cycloaddition substrate of interest was the enynamide analogous to **345** in which the nitrogen atom is protected as a Boc derivative so that the carbamate would be amenable to cleavage under mild acidic conditions in the indoline and indole products. Our synthesis of the Boc-protected enynamide **350** is outlined in Scheme 24. Global silylation of the acid and the

alkyne of **322** followed by chemoselective cleavage of the resulting silyl ester afforded **346** in low yield, reflecting the difficulty in separating the desired carboxylic acid from the silanol byproduct. Modified Curtius rearrangement with DPPA and *t*-BuOH then generated the Boc-carbamate **347** and our alkynylation protocol provided enynamide **348**. Desilylation of the protected acetylene and subsequent conversion to the ester using our optimized protocol finally afforded **350** for our cycloaddition studies.

Scheme 24

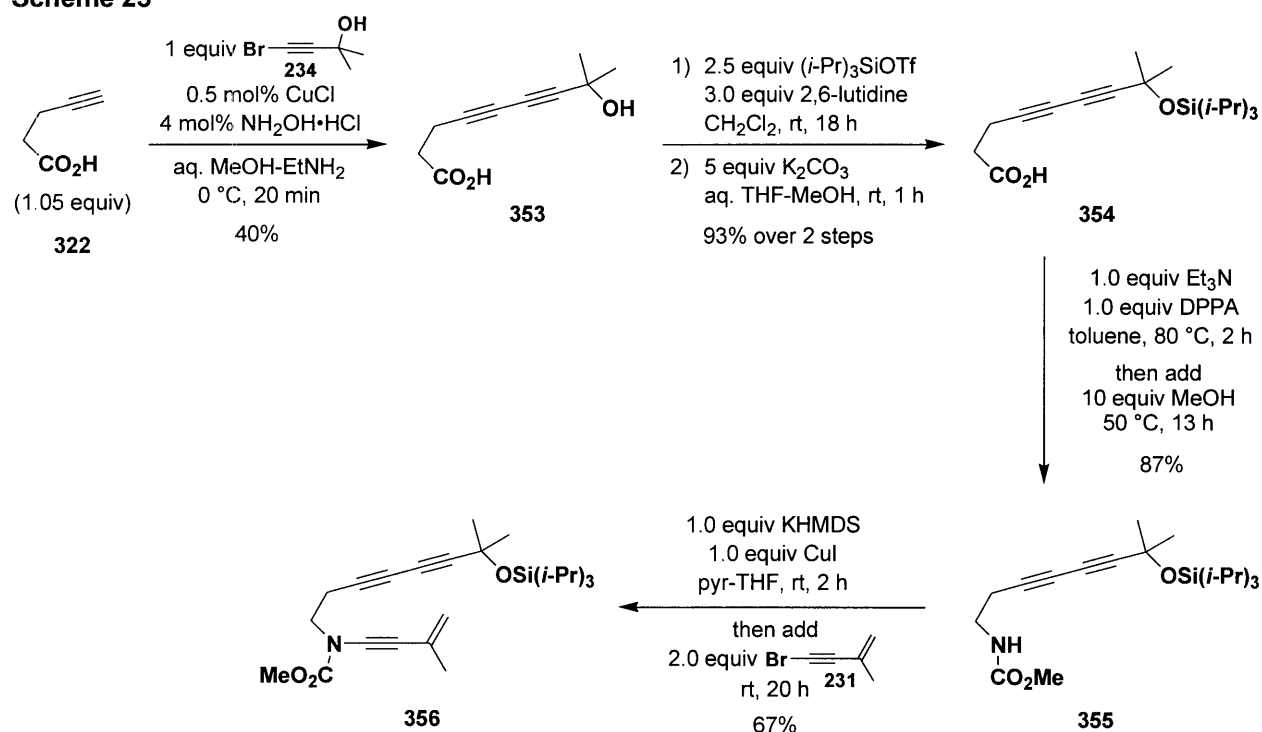


Our next cycloaddition substrate, enynamide **352** in which the 2 π component bears an aryl substituent, was available in two synthetic steps from **323** (eq 87). Sonogashira coupling of the alkyne with iodobenzene provided arenyn **351** and subsequent alkynylation of the carbamate with bromo enyne **231** installed the enyne component for cycloaddition.



The next cycloaddition substrate we targeted was **356** in which a diyne serves as the 2π component and an enynamide as the 4π component. Cadiot-Chodkiewicz coupling of **322** and **234** provided diynoic acid **353** in modest yield, reflecting the competitive consumption of bromoalkyne **234** through homocoupling pathways. The tertiary alcohol was then protected via global silylation of **353** followed by chemoselective cleavage of the silyl ester. Application of the modified Curtius rearrangement protocol with DPPA to **354** afforded carbamate **355** and subsequent alkynylation provided enynamide substrate **356** for cycloaddition.

Scheme 25

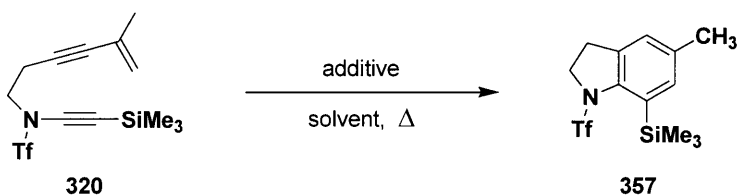


Intramolecular [4 + 2] Cycloaddition of Ynamides and Conjugated Enynes

We initially investigated the feasibility of intramolecular [4 + 2] cycloadditions of ynamides with conjugated enynes using **320** as a test substrate. We were pleased to find that heating **320** in toluene furnished indoline **357** as the major product, and our optimization of temperature revealed that cycloaddition of **320** at 180 °C provides indoline in higher yield than reactions conducted at 150 °C or 210 °C (Table 7, entries 1–3). As discussed in Chapter 2, our enyne cycloadditions typically are performed in the presence of phenolic additives which may

help to suppress the polymerization of these unsaturated compounds at elevated temperatures and may facilitate the isomerization of cyclic allene intermediates to aromatic products via proton or hydrogen atom transfer pathways. We found that the presence of BHT leads to increased yields of indoline without affecting the rate of ynamide consumption, and the efficiency of reaction does not improve further when more than one equivalent of the phenol is added to the reaction mixture (compare entries 2 and 6). Although 4-methoxy-2,6-di-*t*-butylphenol has a higher reduction potential than BHT and thus may be a better hydrogen atom donor, cycloadditions in the presence of either phenol produce **357** with similar efficiency (compare entries 6 and 7). Yields of indoline decrease when BHT is replaced with *p*-nitrophenol (entry 8) or γ -terpinene (entry 9). Finally, toluene is a better medium for cycloaddition than several weakly basic or acidic solvents which we thought might facilitate isomerization of cyclic allenes to aromatic products in the absence of phenolic additives (entries 10–12).

Table 7. Optimization of Conditions for Enyne Cycloaddition^a

				
entry	solvent (0.05 M)	T (°C)	additive	yield (%) ^b
1	toluene	150	3.0 equiv BHT	39
2	toluene	180	3.0 equiv BHT	68-69
3	toluene	210	3.0 equiv BHT	46
4	toluene	180	none	54
5	toluene	180	0.25 equiv BHT	62-64
6	toluene	180	1.0 equiv BHT	72
7	toluene	180	1.0 equiv 4-OMe-2,6- <i>t</i> -Bu-phenol	67
8	toluene	180	1.0 equiv 4-NO ₂ -phenol	54
9	toluene	180	1.0 equiv γ -terpinene	46
10	pyridine	180	none	39
11	Et ₃ N	180	none	47
12	10% <i>t</i> -BuOH in toluene	180	none	39

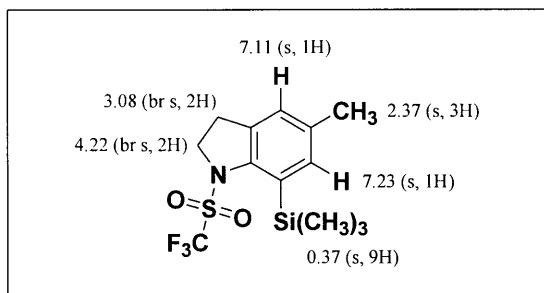
^a Reactions performed on 0.050 g scale. ^b Isolated yields of products purified by column chromatography.

The structural assignment for indoline **357** is based on an analysis of IR and ^1H and ^{13}C NMR data. The IR spectrum shows diagnostic bands for aromatic carbon-carbon double bond stretching at 1583 and 1443 cm^{-1} which is consistent with data reported for *N*-triflyl indolines.^{14c} The IR spectrum also exhibits strong sulfonyl stretching bands at 1137 and 1396 cm^{-1} and a strong carbon-fluorine stretching band at 1224 cm^{-1} . The ^1H NMR spectrum is in good agreement with resonances from previously reported *N*-triflyl indolines:^{14c} the two aromatic protons appear as singlets at 7.11 and 7.23 ppm, the C-5 methyl group appears as a singlet at 2.37 ppm, and the C-7 trimethylsilyl group appears as a singlet at 0.37 ppm. The broadening of resonances for protons nearby to triflamides is established in the literature,¹⁵⁵ and the methylene protons at the C-2 and C-3 positions of indoline **357** appear as broad singlets at 3.08 and 4.22. Resonances from the ^{13}C NMR spectrum are also consistent with data previously reported for indolines.^{14c} There are six signals in the aromatic region between 126.5 and 142.5 ppm, the C-5 methyl group appears at 21.3 ppm, the methyls from the C-7 silyl group appear at 1.0 ppm, and the two methylenes appear at 29.3 and 53.1 ppm. In addition, the signal corresponding to the trifluoromethyl carbon of the sulfonamide appears as a quartet with a J_{CF} value of 327 Hz.

IR (neat):

2956, 1583, 1443, 1396, 1224, 1137, 1032 cm^{-1}

^1H NMR (500 MHz, CDCl_3):



^{13}C NMR (125 MHz, CDCl_3):

142.5, 136.9, 135.9, 135.1, 132.6, 126.5, 120.9 (q, $J_{\text{CF}} = 327$ Hz), 53.1, 29.3, 21.3, 1.0

Table 8 delineates the scope of intramolecular [4 + 2] cycloadditions of conjugated enynes with ynamides. The temperature in each case was optimized for yield after comparing reactions at 30 $^\circ\text{C}$ above and below the conditions listed in Table 8. In addition, the duration of

¹⁵⁵ For previous examples of this resonance broadening from our laboratory, see: (a) Amos, D. T.; Renslo, A. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2003**, *125*, 4970. (b) Maloney, K. M.; Danheiser, R. L. *Org. Lett.* **2005**, *7*, 3115.

each reaction reflects the amount of time necessary for complete consumption of the starting material. The rate of cycloaddition (and other processes which might consume the ynamide) was observed to increase with the strength of the electron-withdrawing group on the nitrogen (compare entries 2 and 7; 3 and 5). In the case of terminal ynamide **358**, the yield improves when conducting the cycloaddition at higher temperatures (compare entries 6–7), perhaps due to less decomposition of the unsubstituted (and relatively unshielded) ynamide via intermolecular

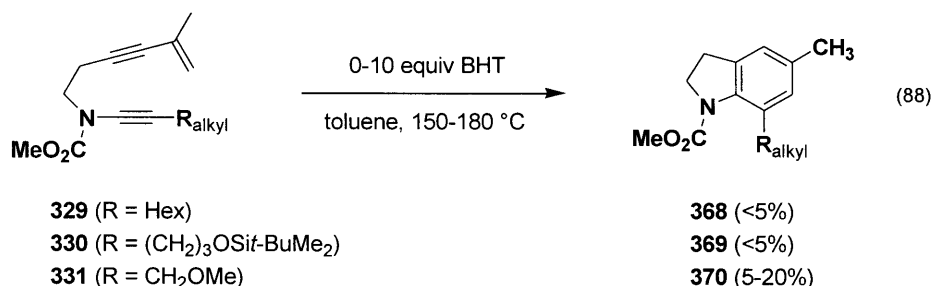
Table 8. [4 + 2] Cycloadditions of Conjugated Enynes with Ynamides

entry	ynamide	conditions ^a	indoline	yield (%) ^b
1	307 (Z = Ts, R = SiMe ₃)	210 °C, 75 min	359	56
2	308 (Z = Ts, R = H)	210 °C, 75 min	360	61
3	320 (Z = Tf, R = SiMe ₃)	180 °C, 5 h	357	68
4	321 (Z = Tf, R = H)	180 °C, 5 h	361	56
5	326 (Z = CO ₂ Me, R = SiMe ₃)	180 °C, 16 h	362	74
6	358^c (Z = CO ₂ Me, R = H)	180 °C, 16 h	363	56
7	358^c (Z = CO ₂ Me, R = H)	210 °C, 2 h	363	71
8	332 (Z = CO ₂ Me, R = C≡CSiMe ₃)	110 °C, 14 h	364	69
9	333 (Z = CO ₂ Me, R = C≡CCH ₂ OSi(<i>i</i> -Pr) ₃)	110 °C, 14 h	365	43
10		110 °C, 8 h	366	76
11		110 °C, 5 h	367	40

^a 3 equiv BHT for Z = Ts, Tf. ^b Isolated yields of products purified by column chromatography. ^c Ynamide **358** was synthesized in 77% yield from **326** with 1.3 equiv TBAF in THF (0 °C, 20 min).

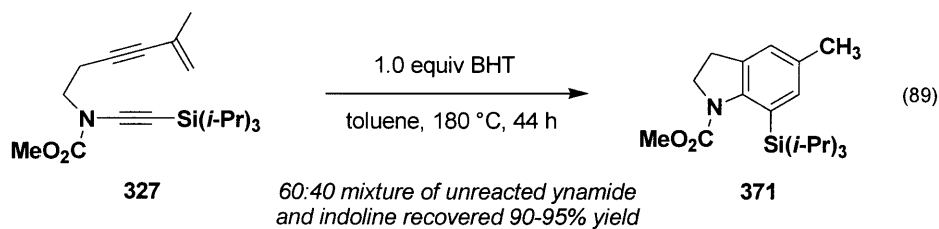
processes.¹⁵⁶ While the cycloadditions of silyl and unsubstituted ynamides require temperatures as high as 180–210 °C, the reactions of diynamides proceed at relatively low temperatures in refluxing toluene. These facile cycloadditions give rise to indolines bearing carbon substituents at the C-7 position and are synthetically significant, since the cycloadducts can be easily elaborated (e.g., by hydrogenation) to furnish indolines that are not available in good yield directly via cycloadditions of ynamides with alkyl substitution (*vide infra*). In addition, to our knowledge these reactions represent the first synthetic applications of diynamides. Finally, we converted a sample of ynamide **335** to its triisopropyl silyl ether and found that the intramolecular cycloaddition of **335** and its silylated derivative both proceed under the same reaction conditions to provide the respective indolines in 40% yield. Therefore, the cycloaddition of **335** does not appear to be affected by the free hydroxyl group of the diynamide.

As mentioned in the previous paragraph, alkyl substitution on the ynamide adversely affects the cycloaddition. Previous work from our laboratory also demonstrated that alkyl substituents on the enynophile sometimes dramatically reduce the efficiency and in some cases the rate of the reaction.^{33c} The cycloadditions of alkyl substituted ynamides under various conditions furnish indolines with C-7 alkyl substituents in poor yield (eq 88). Heating **329–331** under various conditions furnished indolines with C-7 alkyl substituents in poor yield and generated multiple byproducts in minor amounts that we were unable to characterize. It is possible that the poor yields for **368–370** are due to an electronic effect: whereas electron-withdrawing alkynyl and silyl groups on the ynamide appear to activate the substrate for cycloaddition, electron-donating alkyl substituents on the ynamide may impede the cycloaddition by raising the LUMO energy of the 2π component. The difficulty in generating indolines with

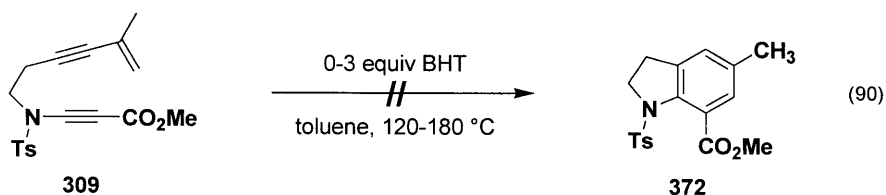


¹⁵⁶ As temperature increases, the activation energy for bimolecular processes increases more than the activation energy increases for unimolecular process. This is due to the relationship of temperature and entropy in the Gibbs free energy equation ($\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$) as $\Delta S^\ddagger_{\text{bimolecular}} < \Delta S^\ddagger_{\text{unimolecular}} < 0$.

C-7 alkyl substituents could also be due to an unfavorable *peri* interaction that develops in the transition state between the alkyl and methoxycarbonyl substituents, which could inhibit the cycloaddition and allow undesired side reactions to compete. Witulski similarly noted that bulky ynamide substituents have a detrimental effect on the rate and efficiency of thermal intramolecular [4 + 2] cycloadditions with dienes.¹⁶ Interestingly, the reaction of ynamide **326** bearing a sterically-demanding trimethylsilyl group proceeds in good yield upon reaction for 16 h at 180 °C (Table 8, entry 5) and does not seem adversely affected by *peri* interactions with the methoxycarbonyl in the transition state. The length of a carbon-silicon σ bond (1.89 Å), however, is considerably longer than a typical carbon-carbon bond (1.54 Å), and the trimethylsilyl group is extended farther from the reactive components of the transition state than alkyl groups. Compared to the cycloaddition of trimethylsilyl ynamide **326**, the reaction of the bulkier triisopropylsilyl ynamide **327** is particularly sluggish (eq 89). A 60:40 mixture of unreacted **327** and indoline **371** was obtained in 90–95% yield in the reaction shown below, and the triisopropylsilyl group which suppressed the rate of cycloaddition also shielded the ynamide from undesirable side reactions which might have consumed the starting material.



Our attempts to generate indoline **372** via cycloaddition of “push-pull” ynamide **309** were unsuccessful. Heating this ynamide under various conditions led to complete decomposition with the formation of multiple byproducts. Former group member Brenda Palucki observed a similar negative result when exploring the cycloaddition of “push-pull” ynamide **179a** for the preparation of a carbazole.^{33c} Recently, Wudl reported the thermal decomposition of these types



of ynamides via migration of the tosyl group at temperatures as low as 100 °C (eq 91).¹⁵⁷ The initial conversion of **373** to **374** appears to be a [1,3] sigmatropic rearrangement, and Wudl speculates that **375** may be formed from intermediate **374** via a second unimolecular rearrangement or intermolecular reactions with another equivalent of ynamide **373**. It is not clear whether our “push-pull” ynamide **309** decomposes through similar processes.

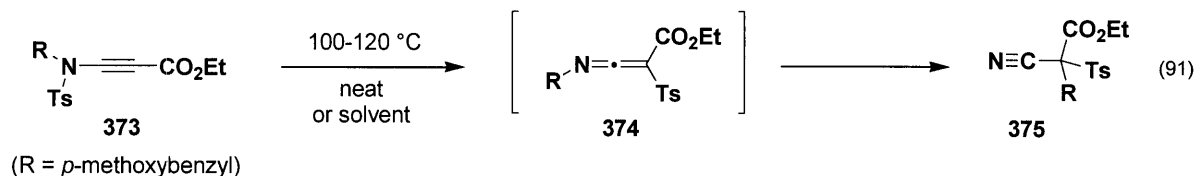


Table 9 delineates the scope of intramolecular [4 + 2] cycloadditions of conjugated enynamides with alkynes. As mentioned earlier, the cycloadditions of these electron-rich enynes provide an efficient route to *C-4 substituted* indolines that is complementary to the reactions

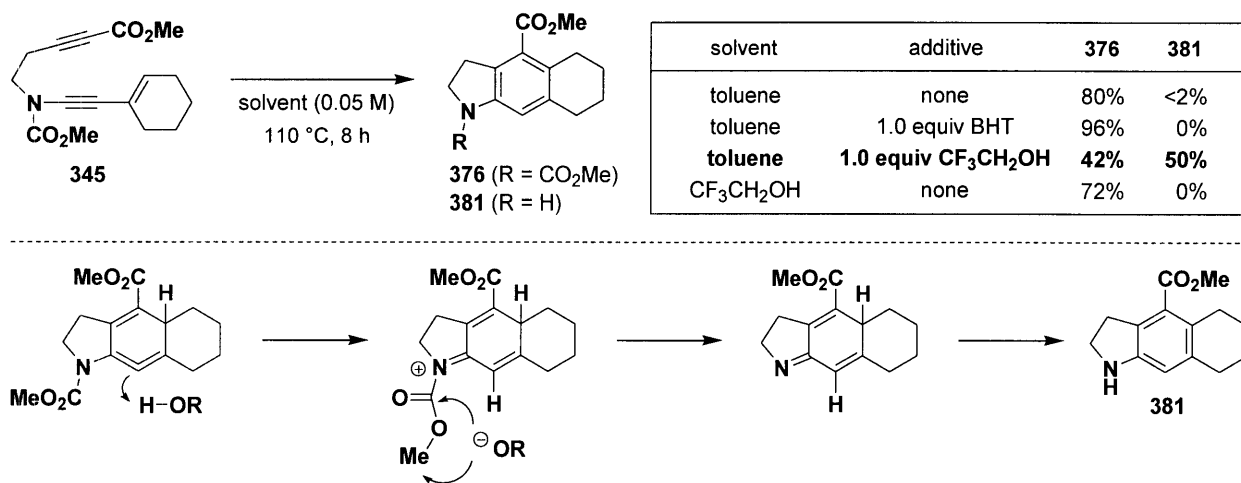
Table 9. [4 + 2] Cycloadditions of Conjugated Enynamides with Alkynes

entry	ynamide	conditions	indoline	yield (%) ^a
1	345 (R = Me)	110 °C, 8 h	376	96
2	345 (R = Me)	110 °C, 8 h ^b	376	80
3	350 (R = <i>t</i> -Bu)	110 °C, 8 h	377	91
4	340 (R = SiMe ₃)	180 °C, 16 h	378	86
5	343 (R = CO ₂ Me)	110 °C, 30 h	379	95
6	356 (R = C≡CC(Me) ₂ OSi(<i>i</i> -Pr) ₃)	110 °C, 30 h	380	84

^a Isolated yields of products purified by column chromatography. ^b Reaction in toluene without BHT.

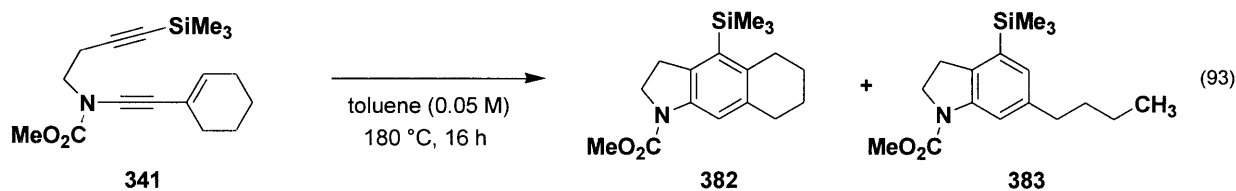
¹⁵⁷ Bendikov, M.; Duong, H. M.; Bolanos, E.; Wudl, F. *Org. Lett.* **2005**, 7, 783.

Scheme 26



trifluoroethoxide species exist as a tight ion pair in toluene, which allows reaction pathways leading to cleavage of the carbamate to compete with deprotonation at the C-5 position. When trifluoroethanol is the solvent for cycloaddition, we believe that solvation of the alkoxide through hydrogen bonding interactions with the protic solvent suppresses the nucleophilicity of the anion and allows elimination pathways leading to protected indoline **376** to occur. It is significant that reactions carried out in the presence of BHT do not produce any indoline **381** in which cleavage of the carbamate has occurred. One explanation is that in this case protonation of the cyclic allene generates a phenoxide counterion that is too bulky to participate in the reactions shown above that may cleave the carbamate group. It is also possible that BHT does not donate a proton to the cyclic allene but rather facilitates isomerization through radical-mediated hydrogen atom transfer pathways.

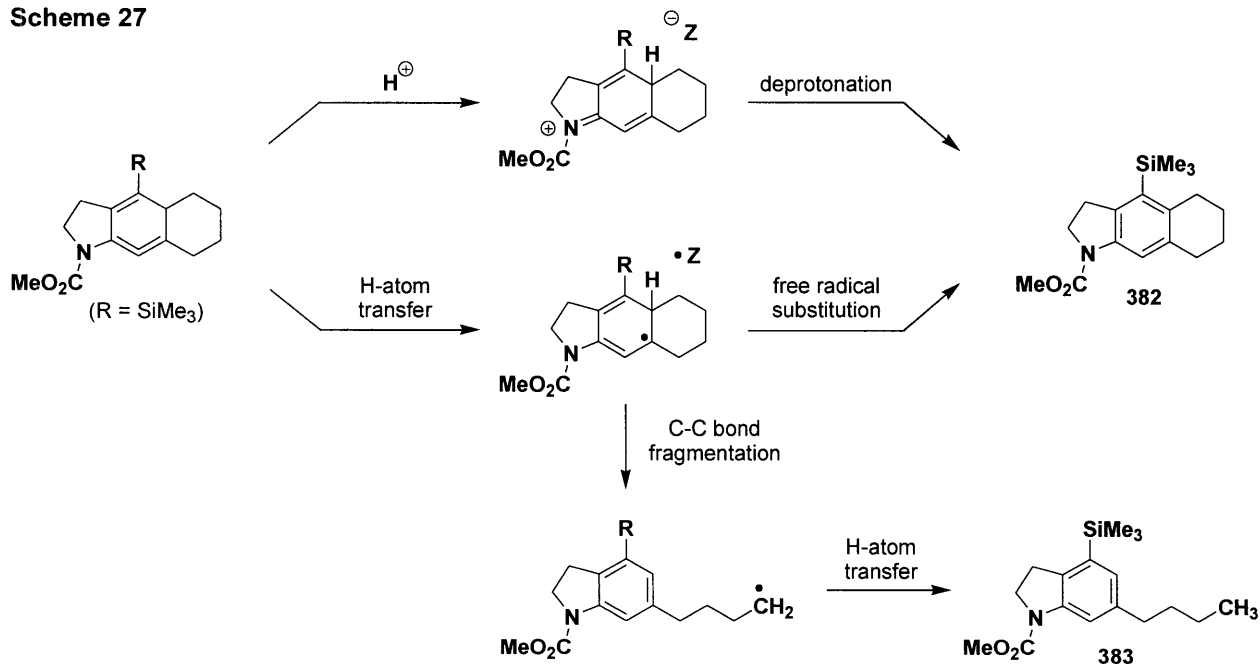
Other observations in the course of our studies of the enynamide cycloaddition suggest that BHT indeed behaves as a hydrogen atom donor in these reactions. Consider the cycloaddition of **341**: heating this ynamide in toluene under various conditions afforded a mixture of indolines **382** and **383** (eq 93). In this case, protonation of the cyclic allene intermediate would generate an N-acyliminium carbocation species and deprotonation at the C-5 position would provide the normal indoline product **382** (Scheme 27). Alternatively, donation of a hydrogen atom to the cyclic allene would lead to a pentadienyl radical and hydrogen atom abstraction from the C-5 position of the pentadienyl radical would then afford **382**. In this case, however, the pentadienyl radical can also aromatize via unimolecular carbon-carbon bond



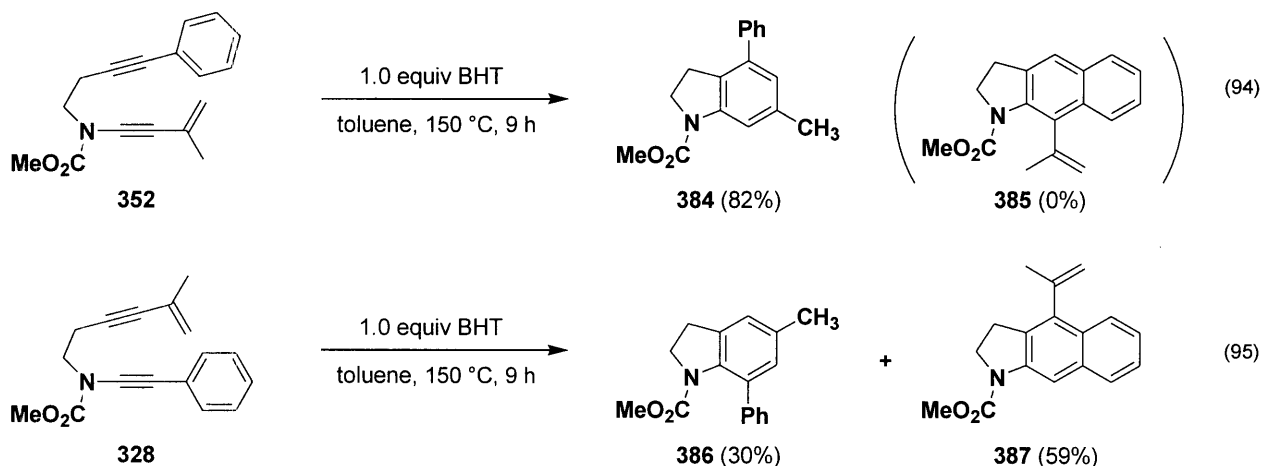
additive	ratio 382 : 383	yield (382 + 383)
none	70 : 30	40%
1.0 equiv BHT	44 : 56	60%

fragmentation leading to a primary radical which can abstract a hydrogen atom to finally afford **383**. More fragmentation product (**383**) is produced in the presence of BHT, which suggests that the phenol might be promoting isomerization via donation of a hydrogen atom to the cyclic allene intermediate. It cannot be overlooked, however, that the combined yield of **382** and **383** is 20% lower in the absence of BHT. It might be possible that the phenol does not affect the ratio of proton to hydrogen atom transfer to the cyclic allene, but rather promotes the formation of **383** by quenching the high energy primary radicals generated by fragmentation that would otherwise decompose through other pathways.

Scheme 27



We concluded our studies on the indoline synthesis by examining the cycloadditions of **352** and **328** (eq 94–95). In each case, two modes of [4 + 2] cycloaddition are possible, one in which an enyne participates as a 4 π component, and the other in which an arenynes acts as the 4 π partner. Heating **352** at 150 °C affords **384** as the product of an enyne cycloaddition in excellent yield. We did not detect **385** in this reaction, presumably due to the high energy of activation required to disrupt aromaticity in the transition state of arenynes cycloadditions. The cycloaddition of **328**, however, affords a 2:1 ratio of separable arenynes cycloaddition product **387** to enyne cycloaddition product **386**. In this case, we believe that the nitrogen activates the arenynes as an electron-rich 4 π component to the extent that arenynes cycloaddition is preferred to enyne cycloaddition despite the disruption of aromaticity in the transition state.

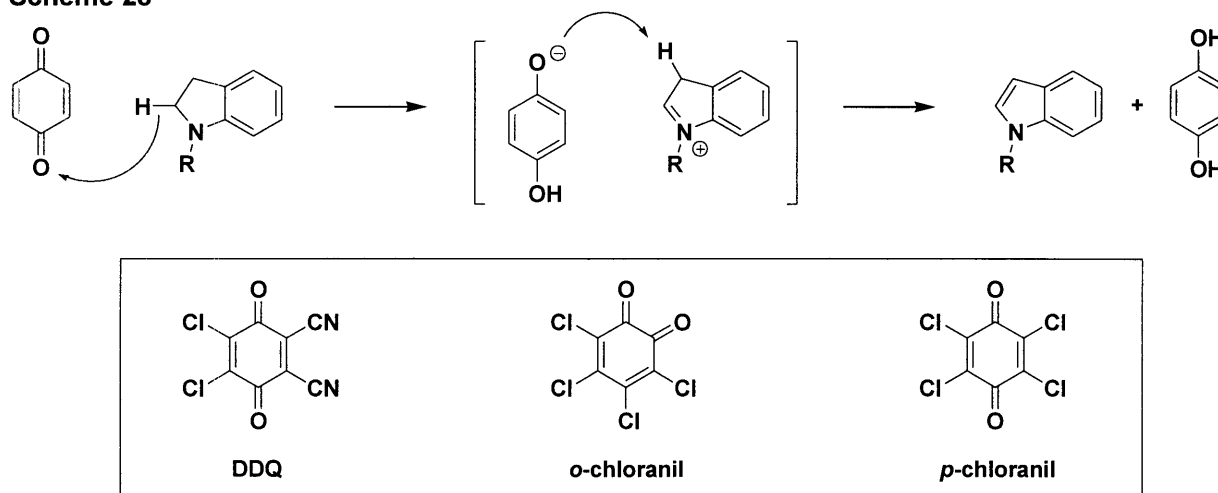


Oxidation of Indolines to Indoles

The oxidation of indolines generated from our enyne cycloadditions was expected to provide access to a variety of indoles highly substituted on the six-membered ring. Several methods are well-established for the conversion of indolines to indoles. Common reagents for this transformation include various quinones, O₂ with cobalt catalysis (salcomine), manganese reagents such as MnO₂ and Mn(OAc)₃, and other transition metal catalysts such as (Ph₃P)₂RuCl₂, CuCl₂, and palladium on carbon.¹⁵⁸ We chose to explore this transformation using quinone reagents such as DDQ and *o*-chloranil, which are popular reagents for the dehydrogenation of

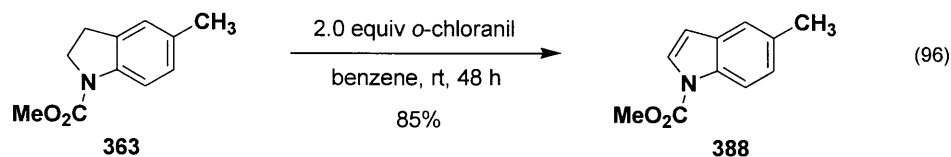
¹⁵⁸ For a review of reagents used to oxidize indolines to indoles, see ref 1a (pp 489–492).

Scheme 28



hydroaromatic compounds.¹⁵⁹ DDQ is the most powerful quinone reagent in routine use and dehydrogenates 1,2-dihydronaphthalene 5500 times faster than *p*-chloranil at 100 °C.¹⁶⁰ *o*-Chloranil is a milder alternative to DDQ; with a lower oxidation potential it effects the dehydrogenation of 1,2-dihydronaphthalene 4200 times faster than *p*-chloranil at 100 °C.¹⁶⁰ The mechanism for oxidation of indolines to indoles using these reagents involves C-2 hydride transfer from the indoline to the quinone via 1,6-addition as shown in the scheme above. The nitrogen atom offers stability to the adjacent C-2 carbocation before deprotonation at the C-3 position furnishes the indole.

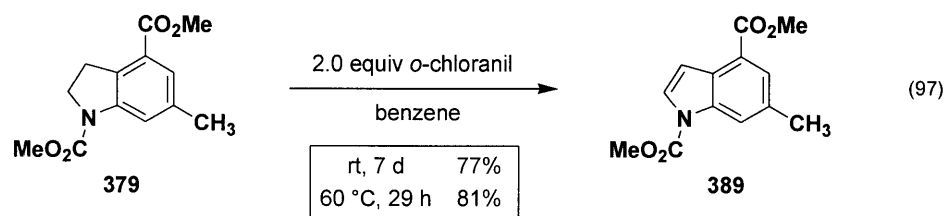
Oxidation of indoline cycloaddition products **363** and **379** was conveniently achieved employing *o*-chloranil in benzene to afford indoles **388** and **389** in good yield (eq 96–97).¹⁶¹ Excess quinone was used to compensate for slow oxidations at room temperature. The reaction of **379** is particularly sluggish at room temperature due to the inductive effect of the C-4 ester. Carrying out the oxidation at 60 °C increases the rate of hydride transfer to the quinone and provides the indole in similar yield.



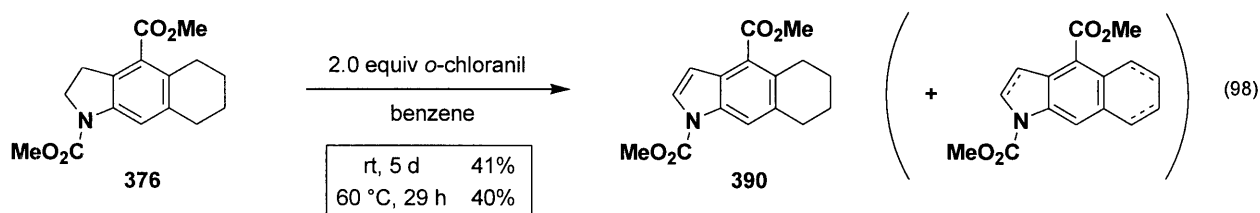
¹⁵⁹ Fu, P. P.; Harvey, R. G. *Chem. Rev.* **1978**, 78, 317.

¹⁶⁰ Jackman, L. M. *Adv. Org. Chem.* **1960**, 2, 329. Reviewed in ref 159.

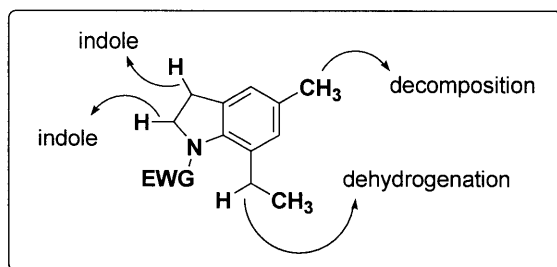
¹⁶¹ For examples of the oxidation of indolines to indoles using *o*-chloranil, see: (a) Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1996**, 61, 2594. (b) Bailey, W. F.; Jiang, X.-L. *J. Org. Chem.* **1996**, 61, 2596.



The oxidation of **376** (eq 98) was not as straightforward as the two cases shown above. Partial dehydrogenation of the cyclohexyl ring is observed under our previous optimized conditions, and the desired indole **390** is obtained in only modest yield. We found that oxidation of the six-membered ring occurs at a rate similar to dehydrogenation of the five-membered ring, and therefore the undesired oxidation of the cyclohexyl ring could not be avoided by using only one equivalent of *o*-chloranil.

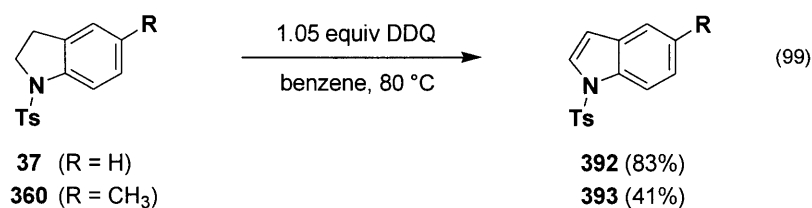


The competing oxidation of the six-membered ring in **376** is not surprising when one considers the mechanism of quinone dehydrogenation. When the indoline nitrogen bears an electron-withdrawing group, the activation energy for C-2 hydride transfer to the quinone increases to the extent that competitive hydride transfers from benzylic sites can occur. Abstraction of hydride from the C-3 methylene of an electron-deficient indoline would still provide the indole. Problems can arise, however, when the indoline has alkyl substituents with hydrogen atoms that are benzylic to the six-membered ring. As shown below, hydride transfer from the C-5 methyl group would lead to decomposition after formation of a benzylic



carbocation. Abstraction of hydride from the methylene attached to the C-7 position of the indoline would also generate a benzylic carbocation; in this case, however, dehydrogenation can occur via deprotonation of the adjacent methyl group to provide a vinyl group. Hydride abstraction from the C-7 substituent should be more facile than abstraction from the C-5 methyl group, as the former would generate a secondary carbocation that is more stable than the primary carbocation generated from the latter process. This rationale might partially explain why the oxidations of **363** and **379**, two indolines with a methyl group on the six-membered ring, proceed more efficiently than the oxidation of **376**, an indoline with a fused cyclohexyl ring. In addition, it cannot be overlooked that indoline **376** has more benzylic hydrogens (four from the C-5 and C-6 positions) than indolines **363** or **379** (each with three from the methyl group),¹⁶² which should statistically increase the susceptibility of **376** to undesired hydride abstractions relative to **363** and **379**.

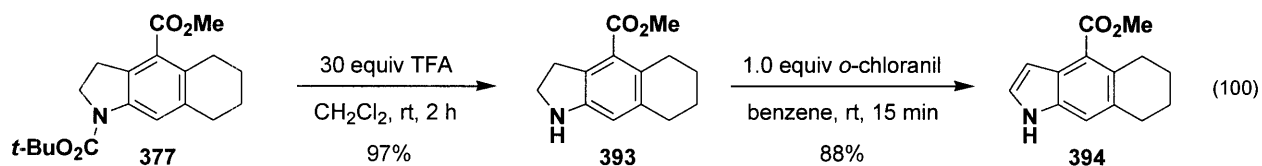
Our results of the oxidation of **37** and **360** with DDQ confirm that alkyl substituents bearing hydrogen atoms benzylic to the six-membered ring have a dramatic effect on the efficiency of oxidation (eq 99). Whereas the dehydrogenation of **37** (R = H) proceeded smoothly, the oxidation of **360** (R = CH₃) provided indole **392** in only modest yield. In this case, we speculate that competitive hydride transfer from the C-5 methyl group led to decomposition of the indoline.



To avoid the oxidation of the fused cyclohexyl ring of indolines such as **376**, we decided first to remove the electron-withdrawing group from the nitrogen. We believed that the free amine would have a greater ability to stabilize a C-2 carbocation and thus promote the desired oxidation pathway over competitive hydride transfer. Cleavage of the Boc carbamate of indoline **377** with trifluoroacetic acid provided deprotected indoline **393** (eq 100). Treatment of **393** with

¹⁶² These totals do not include the two benzylic hydrogens at the C-3 position, as hydride transfer from this site would furnish desired the indole.

one equivalent of *o*-chloranil chemoselectively provides indole **394** in excellent yield without dehydrogenation of the cyclohexyl ring. Under these conditions, the oxidation of **393** is complete after 15 min and is much faster than similar reactions of *N*-methoxycarbonyl indolines with excess quinone (eq 96–98).



Summary

The intramolecular [4 + 2] cycloadditions of conjugated enynes with ynamides and conjugated enynamides with alkynes are complementary reactions that provide highly substituted indolines. Our strategy offers a divergent synthesis of indolines and indoles with regiocontrolled access to various substituents on the six-membered ring. Application of our copper-mediated alkynylation protocol to homopropargyl amide derivatives allowed for the facile preparation of cycloaddition substrates from readily available starting materials. Oxidation of the indoline products then provides highly substituted indoles.

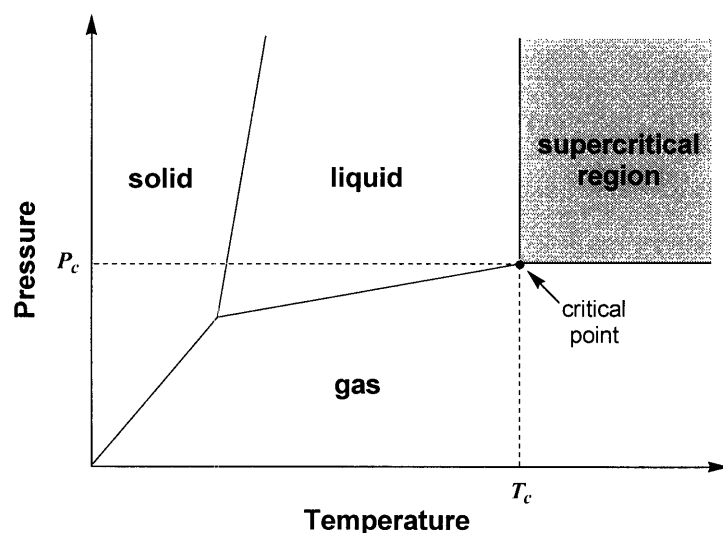
Part II

Synthesis of Nitrogen Heterocycles in Supercritical Carbon Dioxide

Chapter 1

Introduction: Carbon-Nitrogen Bond-Forming Reactions in Supercritical Carbon Dioxide

Supercritical carbon dioxide (scCO₂) has attracted considerable attention in recent years as an alternative to conventional solvents for organic synthesis.¹⁶³ This interest has been motivated by environmental and health considerations, as carbon dioxide is relatively nontoxic and nonflammable, inexpensive and widely available, and poses minimal problems with regard to waste disposal. In addition, the critical temperature (T_c) for carbon dioxide is 31 °C, which allows the use of scCO₂ as a solvent for reactions performed at mildly elevated temperatures.



	T_c (°C)	P_c (bar)
xenon	17	58
CHF ₃	26	49
CO₂	31	74
ammonia	133	112
hexane	234	30
methanol	239	81
water	374	220

Aside from these practical advantages, the unique solvent properties of scCO₂ have also attracted interest. Supercritical fluids share the characteristics of both gases and liquids. For example, scCO₂ has the low viscosity of a gas that allows for greater diffusion of solvated

¹⁶³ (a) Oakes, R. S.; Clifford, A. A.; Rayner, C. M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 917. (b) Tester, J. W.; Danheiser, R. L.; Weinstein, R. D.; Renslo, A.; Taylor, J. D.; Steinfeld, J. I. In *Green Chemical Syntheses and Processes*; Anastas, P. T., Heine, L. G., Williamson, T. C., Eds.; Washington, D.C.: Oxford University Press, 2000. pp 270–291. (c) Jessop, P. G.; Leitner, W. *Chemical Synthesis Using Supercritical Fluids*; Wiley-VCH: Weinheim-New York, 1999. (d) Leitner, W. *Topp. Curr. Chem.* **1999**, 206, 107.

compounds and thus faster rates for diffusion-controlled reactions. This medium also exhibits the high compressibility of a gas. Supercritical CO₂ has the solvating ability of a liquid, however, and can dissolve various organic compounds, particularly nonpolar and fluorinated molecules. Near the critical point, relatively small changes in pressure (and temperature) lead to significant changes in viscosity, density, and self-diffusivity, and in some cases, the tunable solvent power of scCO₂ allows for the separation of reagents and products through simple changes in reaction conditions.¹⁶⁴ Finally, reactions conducted near the critical point sometimes proceed with different selectivities than otherwise observed in conventional media.¹⁶⁵

The successful application of scCO₂ as a reaction solvent for a variety of synthetic transformations is now well-documented. In previous collaborations with the laboratory of Jefferson W. Tester in the MIT Department of Chemical Engineering, our research group has reported on the rates and selectivities of Diels-Alder cycloadditions in scCO₂^{166,167,168} and the rate-accelerating effects of CO₂-water emulsions for hydrolysis reactions in this relatively nonpolar medium.¹⁶⁹ Other researchers have explored the regioselectivity of dipolar cycloadditions in this green solvent.¹⁷⁰ Supercritical CO₂ has replaced conventional solvents for a number of palladium-catalyzed reactions¹⁷¹ and other transition-metal-mediated processes.¹⁷²

¹⁶⁴ Zosel, K. *Angew. Chem. Int. Ed.* **1978**, *17*, 702.

¹⁶⁵ For examples, see: (a) Fürstner, A.; Koch, D.; Langemann, K.; Leitner, W.; Six, C. *Angew. Chem. Int. Ed.* **1997**, *36*, 2466. (b) Oakes, R. S.; Clifford, A. A.; Bartle, K. D.; Pett, M. T.; Rayner, C. M. *Chem. Commun.* **1999**, 247. For unusual regioselectivities in Diels-Alder cycloadditions that could not be reproduced by our laboratory (ref 166b), see: (c) Ikushima, Y.; Saito, N.; Arai, M. *J. Phys. Chem.* **1992**, *96*, 2293.

¹⁶⁶ (a) Weinstein, R. D.; Renslo, A. R.; Danheiser, R. L.; Harris, J. G.; Tester, J. W. *J. Phys. Chem.* **1996**, *100*, 12337. (b) Renslo, A. R.; Weinstein, R. D.; Tester, J. W.; Danheiser, R. L. *J. Org. Chem.* **1997**, *62*, 4530. (c) Weinstein, R. D.; Renslo, A. R.; Danheiser, R. L.; Tester, J. W. *J. Phys. Chem. B* **1999**, *103*, 2878.

¹⁶⁷ Renslo, A. R. Ph. D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, June 1994.

¹⁶⁸ For other studies, see: (a) Clifford, A. A.; Pople, K.; Gaskill, W. J.; Bartle, K. D.; Rayner, C. M. *J. Chem. Soc., Chem. Commun.* **1997**, 595. (b) Clifford, A. A.; Pople, K.; Gaskill, W. J.; Bartle, K. D.; Rayner, C. M. *J. Chem. Soc., Faraday Trans.* **1998**, *94*, 1451. (c) Oakes, R. S.; Heppenstall, T. J.; Shezad, N.; Clifford, A. A.; Rayner, C. M. *Chem. Commun.* **1999**, 1459.

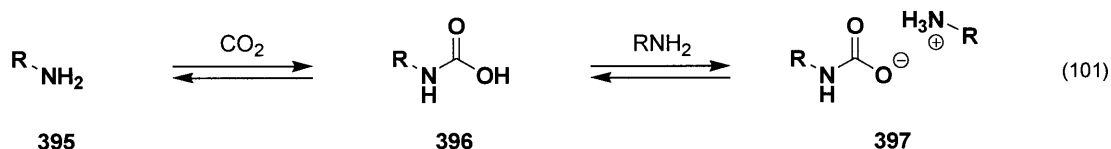
¹⁶⁹ Timko, M. T.; Diffendal, J. M.; Tester, J. W.; Smith, K. A.; Peters, W. A.; Danheiser, R. L.; Steinfeld, J. I. *J. Phys. Chem. A* **2003**, *107*, 5503.

¹⁷⁰ (a) Totoe, H.; McGowin, A. E.; Turnbull, K. *J. Supercrit. Fluid* **2000**, *18*, 131. (b) McGowin, A. E.; Jackson, L.; Marshall, L. W.; Turnbull, K. *Org. Prep. Proc. Int.* **2001**, *33*, 100. (c) Lee, C. K. Y.; Holmes, A. B.; Al-Duri, B.; Leeke, G. A.; Santos, R. C. D.; Seville, J. P. K. *Chem. Commun.* **2004**, 2622.

¹⁷¹ (a) Carroll, M. A.; Holmes, A. B. *Chem. Commun.* **1998**, 1395. (b) Morita, D. K.; Pesiri, D. R.; David, S. A.; Glaze, W. H.; Tumas, W. *Chem. Commun.* **1998**, 1397. (c) Shezad, H.; Oakes, R. S.; Clifford, A. A.; Rayner, C. M. *Tetrahedron Lett.* **1999**, *40*, 2221. (d) Early, T. R.; Gordon, R. S.; Carroll, M. A.; Holmes, A. B.; Shute, R. E.; McConvey, I. F. *Chem. Commun.* **2001**, 1966. (e) Gordon, R. S.; Holmes, A. B. *Chem. Commun.* **2002**, 640. (f) Ley, S. V.; Ramarao, C.; Gordon, R. S.; Holmes, A. B.; Morrison, A. J.; McConvey, I. F.; Shirley, I. M.; Smith, S. C.; Smith, M. D. *Chem. Commun.* **2002**, 1134. (g) Smith, C. J.; Early, T. R.; Holmes, A. B.; Shute, R. E. *Chem. Commun.* **2004**, 1976. (h) Smith, C. J.; Tsang, M. W. S.; Holmes, A. B.; Danheiser, R. L.; Tester, J. W. *Org. Biomol. Chem.* **2005**, in press.

Other useful transformations that can be achieved in this green solvent include a number of oxidation reactions,¹⁷³ catalytic hydrogenation,¹⁷⁴ olefin metathesis,^{165a,175} and enzyme-catalyzed organic reactions.¹⁷⁶ In addition, scCO₂ has been used in a number of commercial applications.¹⁷⁷

To date, however, only a few examples have been reported of carbon-nitrogen bond formation in scCO₂, principally due to the facility of the reaction of amines with this electrophilic solvent. The addition of amines to carbon dioxide forms carbamic acids of type **396** and ammonium carbamate salts of type **397**,¹⁷⁸ and this facile process poses a significant challenge that complicates the synthesis of nitrogen heterocycles in scCO₂. Sterically-demanding or electron-withdrawing substituents on the amine can suppress carbamic acid formation,^{178c} although these protective groups may also inhibit the reactivity of amines in desired processes.



As previously mentioned, scattered reports have demonstrated successful carbon-nitrogen bond-forming reactions in scCO₂. For example, Noyori developed a process for the synthesis of formamides via ruthenium-catalyzed hydrogenation of carbon dioxide in the presence of amines (eq 102).¹⁷⁹ Noyori proposed that the formic acid generated from the reduction of CO₂ reacts with amines to provide formamides via ammonium formate intermediates. Noyori observed that

¹⁷² For a review, see: Leitner, W. *Acc. Chem. Res.* **2002**, 35, 746.

¹⁷³ For a review, see: Campestrini, S.; Tonellato, U. *Curr. Org. Chem.* **2005**, 9, 31.

¹⁷⁴ Kainz, S.; Brinkmann, A.; Leitner, W.; Pfaltz, A. *J. Am. Chem. Soc.* **1999**, 121, 6421.

¹⁷⁵ Fürstner, A.; Ackermann, L.; Beck, K.; Hori, H.; Koch, D.; Langemann, K.; Liebl, M.; Six, C.; Leitner, W. *J. Am. Chem. Soc.* **2001**, 123, 9000.

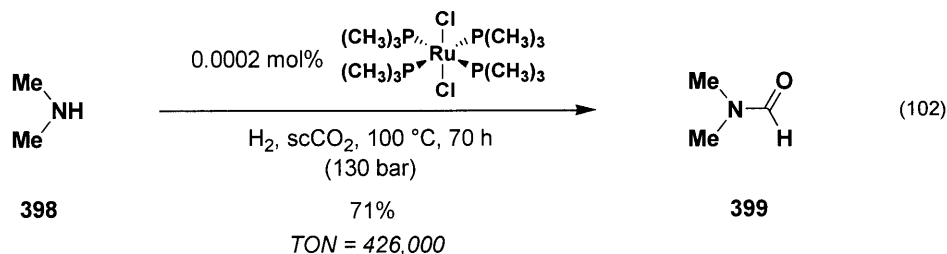
¹⁷⁶ For a review, see: Matsuda, T.; Harada, T.; Nakamura, K. *Green Chem.* **2004**, 6, 440.

¹⁷⁷ (a) McCoy, M. *Chem. Eng. News* **1999**, 77 (June 14), 11. (b) Wells, S.; DeSimone, J. M. *Angew. Chem. Int. Ed.* **2001**, 40, 518.

¹⁷⁸ (a) Aresta, M.; Ballivet-Tkatchenko, D.; Dell'Amico, D. B.; Bonnet, M. C.; Boschi, D.; Calderazzo, F.; Faure, R.; Labella, L.; Marchetti, F. *Chem. Commun.* **2000**, 1099. (b) Dell'Amico, D. B.; Calderazzo, F.; Labella, L.; Marchetti, F.; Pampaloni, G. *Chem. Rev.* **2003**, 103, 3857. (c) Fischer, H.; Gyllenhaal, O.; Vessman, J.; Albert, K. *Anal. Chem.* **2003**, 75, 622. Also see ref 174.

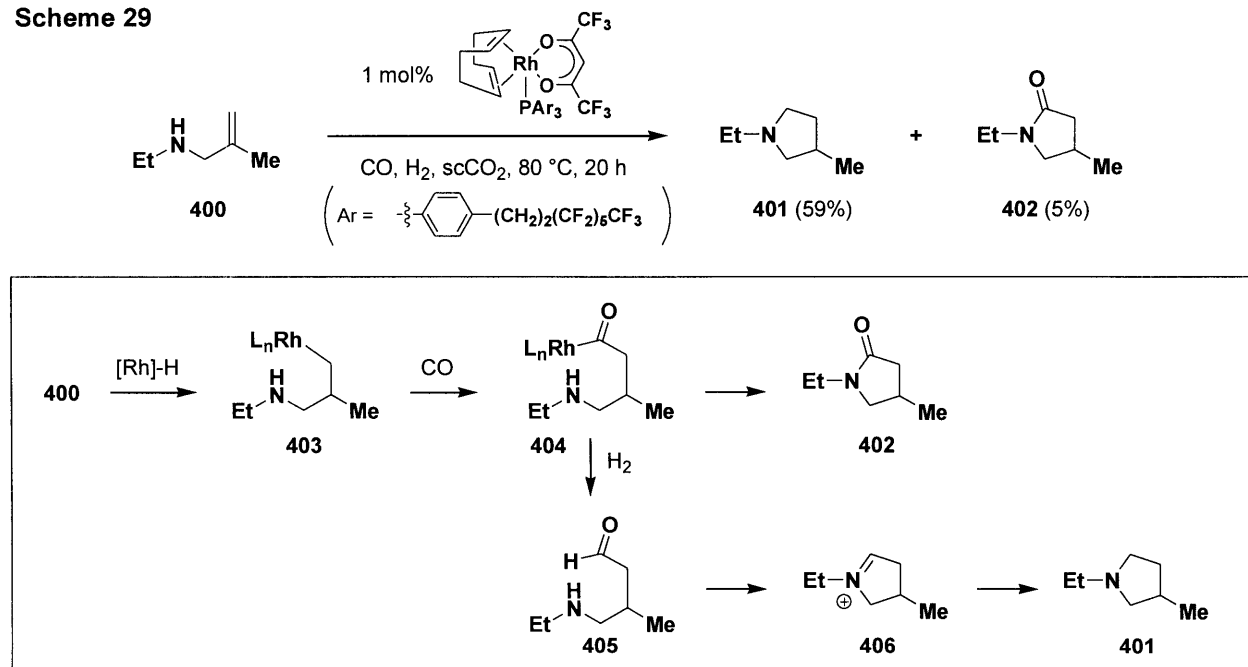
¹⁷⁹ (a) Jessop, P. G.; Hsiao, Y.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1994**, 116, 8851. (b) Jessop, P. G.; Hsiao, Y.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, 118, 344.

the efficiency of the ruthenium catalyst in scCO₂ is higher than in previous transition-metal-catalyzed hydrogenations of CO₂ carried out in amine solvents.



The intramolecular hydroaminomethylation of allylic amines as reported by Leitner is another carbon-nitrogen bond-forming reaction which has been conducted in scCO₂ (Scheme 29).¹⁸⁰ This transformation proceeds via intermediate **403** after olefin insertion of **400** to a rhodium hydride species bearing fluorinated ligands that solubilize the metal complex in scCO₂. Carbon monoxide insertion into **403** generates the acylrhodium species **404**. When this reaction is carried out in conventional solvents, the amino group in **404** intercepts the acylrhodium complex to furnish lactam **402**. In scCO₂, however, **404** is converted instead to

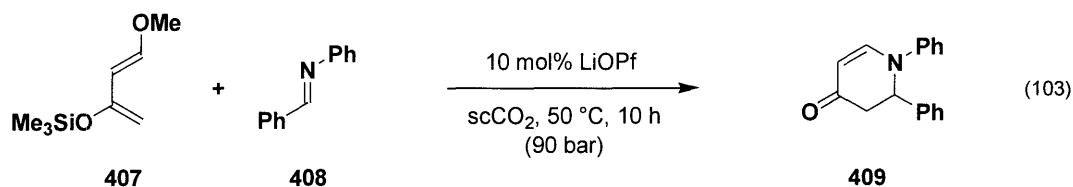
Scheme 29



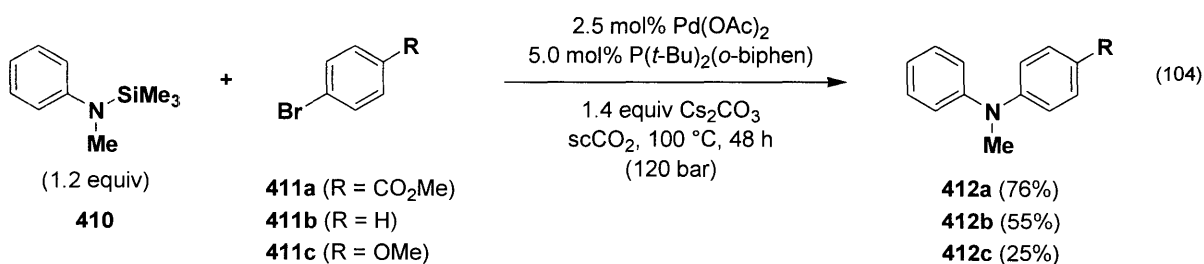
¹⁸⁰ Wittmann, K.; Wisniewski, W.; Mynott, R.; Leitner, W.; Kranemann, C. L.; Rische, T.; Eilbracht, P.; Kluwer, S.; Ernsting, J. M.; Elsevier, C. J. *Chem. Eur. J.* **2001**, 7, 4584.

aldehyde **405** and subsequent reductive amination generates **401**. Leitner attributed this switch in selectivity to the reversible conversion of amine intermediates to carbamic acids and ammonium carbamate salts that impedes reaction pathways leading to the lactam. Thus, the carbon dioxide was serving as both solvent and protecting group for the amine in this reaction.

Shi extended the scope of carbon-nitrogen bond-forming reactions in scCO₂ with a recent report on imino-Diels-Alder reactions in this green solvent (eq 103).¹⁸¹ Cycloadditions of imines with Danishefsky's diene (**407**) in scCO₂ were found to be promoted by Lewis acids such as lithium perfluorooctane sulfonate (LiOPf) to provide vinylogous amides such as **409**. The perfluorinated alkyl chain of the Lewis acid enhances the solubility of the catalyst in scCO₂. Shi did not mention the formation of carbamic acid derivatives via reactions of imine **408** with carbon dioxide, and it is likely that the sp²-hybridized nitrogen bearing an aryl substituent is not sufficiently nucleophilic for addition to the electrophilic solvent.

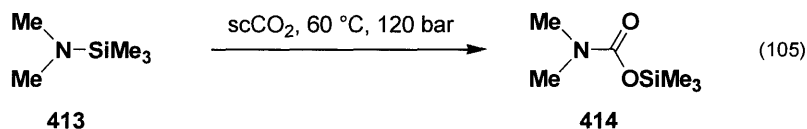


Recently, Holmes developed protocols in collaboration with our laboratory for palladium-catalyzed aminations of aryl halides that replace conventional solvents such as toluene with scCO₂ (eq 104).^{171g,h} The amines under these conditions are protected by a trimethylsilyl group to avoid complications from carbamic acid formation, and reactions proceed via transmetalation of the nitrogen from silicon to palladium. While *N*-silyl anilines such as **410** participate in the coupling reaction, Holmes reported that more nucleophilic *N*-silyl amines such

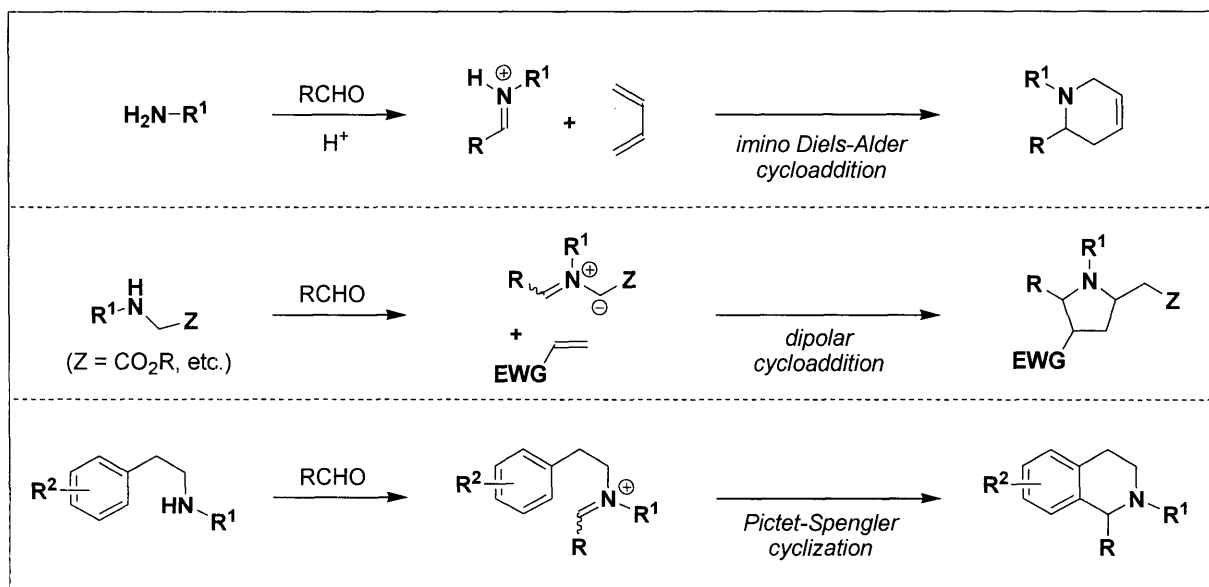


¹⁸¹ Shi, M.; Cui, S.-C.; Li, Q.-J. *Tetrahedron* **2004**, *60*, 6163.

as **413** are converted to silyl carbamates of type **414** via reaction pathways involving addition of the amine to carbon dioxide (eq 105).



Despite these scattered reports, when we began our studies there were no strategies for the utilization of amines in carbon dioxide that would allow for the development of a wide range of carbon-nitrogen bond-forming reactions in scCO₂. Motivated by the significance of nitrogen-containing compounds and the continuing commercial interest in environmentally-friendly and cost-efficient solvents, we developed a program to explore the synthesis of nitrogen heterocycles in scCO₂, focusing, in particular, on reactions proceeding via iminium ion intermediates. Our strategy would employ protective groups to shield amines from carbon dioxide without suppressing various carbon-nitrogen bond-forming reactions such as imino Diels-Alder cycloadditions, dipolar cycloadditions, and Pictet-Spengler cyclizations. The research presented in the next chapter was conducted in collaboration with the laboratories of Andrew B. Holmes from Cambridge University and Jefferson W. Tester from the MIT Department of Chemical Engineering.

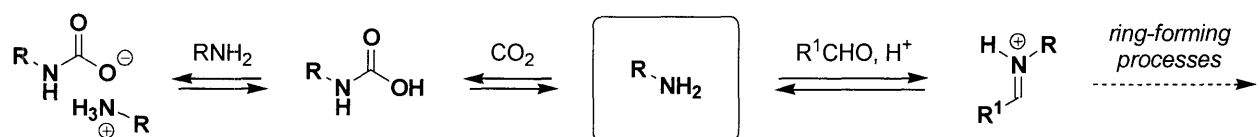


Chapter 2

Iminium Ion Reactions in Supercritical Carbon Dioxide for the Synthesis of Nitrogen Heterocycles

As discussed in the previous chapter, the overall goal of our collaborative project with the Holmes and Tester laboratories was to develop general strategies that would allow the use of scCO_2 as a “green” reaction medium for a variety of carbon-nitrogen bond-forming reactions. At the outset of this project, it was decided that work at Cambridge University would focus on palladium-catalyzed amination reactions (*vide supra*), while studies at MIT would focus on the synthesis of nitrogen heterocycles, particularly by employing various reactions of iminium ions.

Previously, almost no progress had been reported on the synthesis of nitrogen heterocycles in scCO_2 . As discussed in the previous chapter, a serious obstacle to carrying out reactions of amines in carbon dioxide is the facility of their reaction with the electrophilic solvent. In order to achieve efficient carbon-nitrogen bond-forming reactions in scCO_2 , we thought it would be necessary to install a protective group on the amine that would suppress carbamic acid formation and shift the equilibrium shown below in favor of the iminium ion we hoped to employ in the various carbon-nitrogen bond-forming processes.



Imino Diels-Alder Cycloadditions in Supercritical Carbon Dioxide

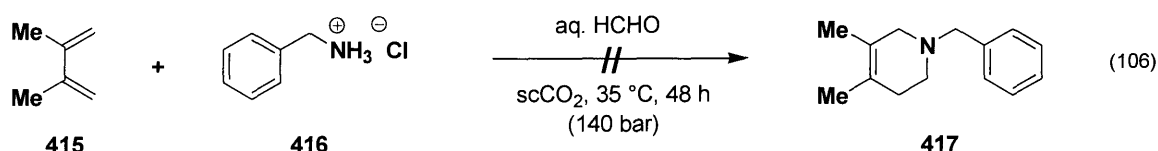
Our initial studies on the synthesis of nitrogen heterocycles in scCO_2 focused on the assembly of tetrahydropyridines via imino Diels-Alder cycloadditions of dienes with iminium dienophiles.¹⁸² Grieco previously developed green conditions for this transformation using water

¹⁸² For a review of imino Diels-Alder reactions, see: (a) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, 57, 6099. (b) Tietze, L. F.; Ketschau, G. *Top. Curr. Chem.* **1997**, 189, 1. (c) Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; San Diego: Academic Press, 1987.

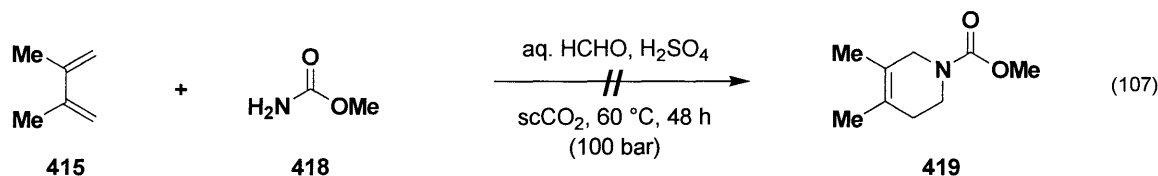
as a solvent; however, these reactions are often sluggish due to the poor solubility of certain dienes and aliphatic aldehydes in the aqueous media.^{183,184} We believed that scCO₂ would be an attractive alternative to water as an environmentally-friendly solvent that would better solubilize nonpolar reagents.

Reactions were carried out in a Thar stainless steel view cell reactor (25 mL internal volume) that allows visual inspection via two coaxial sapphire windows. Cell pressure and temperature were monitored with a pressure gauge and internal thermocouple probe. Temperature set-points were achieved using a controller interfaced with insulated heating tape wrapped tightly about the exterior cell wall. The vessel was placed on a magnetic stir plate and reactor contents were mixed using a magnetic stir bar. Further details on the reactor are provided in the Experimental Section.

Unfortunately, the reaction of benzylamine with formaldehyde using scCO₂ led to a mixture of oligomeric products and none of the desired tetrahydroisoquinoline (eq 106). This result was not surprising, as benzylamine is known to react with carbon dioxide to form



carbamic acids and ammonium carbamate salts,^{174,178c} and these products could further react with formaldehyde in condensation pathways. We attempted to employ carbamate **418** as a less nucleophilic amine that we expected might be inert to carbon dioxide; however, we only observed polymerization of the diene under the reaction conditions shown in eq 107 and were



¹⁸³ (a) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768. (b) Grieco, P. A.; Larsen, S. D. *J. Org. Chem.* **1986**, *51*, 3553. (c) Grieco, P. A.; Parker, D. T.; Fobare, W. F.; Ruckle, R. *J. Am. Chem. Soc.* **1987**, *109*, 5859. (d) Grieco, P. A.; Bahsas, A. *J. Org. Chem.* **1987**, *52*, 5746. (e) Grieco, P. A.; Parker, D. T. *J. Org. Chem.* **1988**, *53*, 3658.

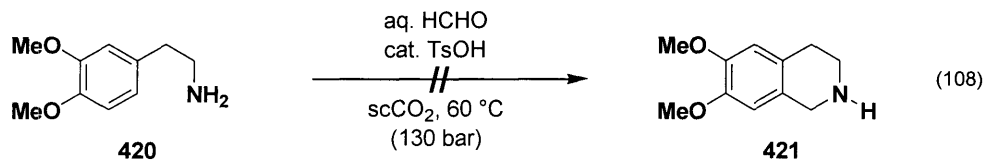
¹⁸⁴ For a report describing the sluggishness of imino Diels-Alder reactions in water on industrial scale, see: Ripin, D. H. B., et al. *Org. Process Res. Dev.* **2003**, *7*, 115.

not able to detect the desired product **419**. It is possible that under these conditions an insufficient concentration of iminium ion is produced to compete with acid-catalyzed polymerization of the diene.

Pictet-Spengler Cyclizations: Intramolecular Reactions of Iminium Ions

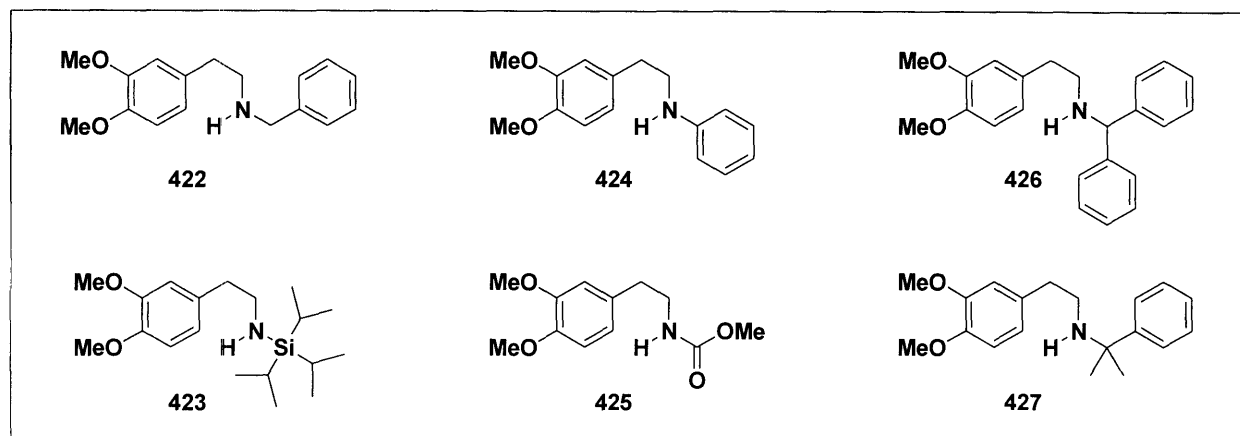
At this stage, we decided to undertake a systematic investigation of strategies to suppress carbamic acid formation. Since intramolecular processes are more facile than intermolecular reactions, we decided to focus our studies on an intramolecular carbon-nitrogen bond-forming reaction, namely the Pictet-Spengler cyclization. The Pictet-Spengler reaction is a valuable method for the synthesis of isoquinoline and indole alkaloids.¹⁸⁵ The valuable medicinal properties associated with tetrahydroisoquinolines and tetrahydro- β -carbolines continue to fuel interest in the synthesis of these classes of heterocycles. In the Pictet-Spengler reaction, these ring systems are produced via the cyclization of iminium ions generated in situ by the condensation of aldehydes with β -arylethylamines. Electron-donating groups on the aromatic ring facilitate addition of the π bond to the iminium ion.

Our initial attempts to achieve Pictet-Spengler reactions in scCO_2 were unsuccessful. The reaction of **420** with carbon dioxide and formaldehyde leads to mixtures of oligomeric products analogous to those generated in failed imino Diels-Alder reactions in scCO_2 . To

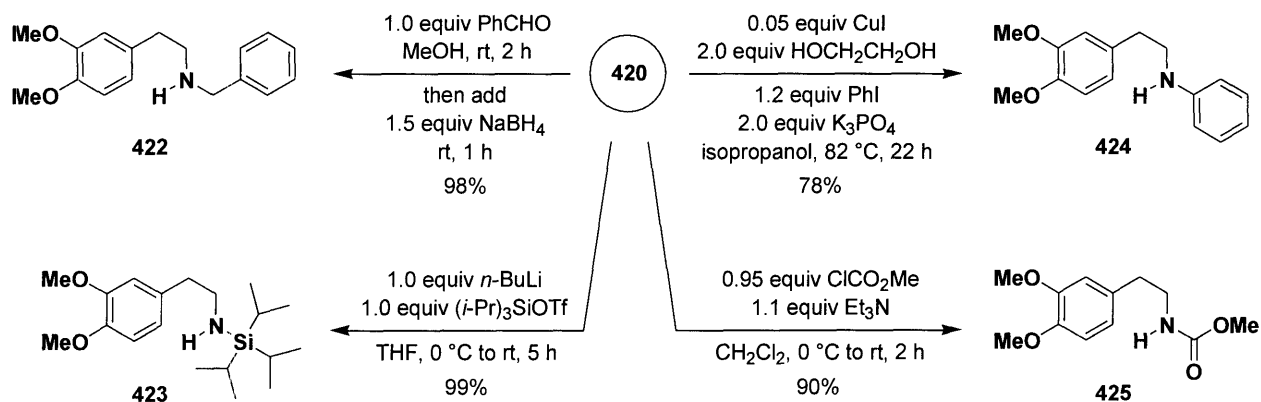


suppress these undesired reaction pathways involving the addition of **420** to carbon dioxide, we considered a number of amine derivatives (**422–427**) that bear sterically-demanding or electron-withdrawing substituents on the nitrogen atom to shield the heteroatom from the electrophilic solvent. To date, we have investigated the reactions of amines **422–425**, each of which was easily prepared as outlined in Scheme 30.

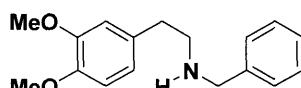
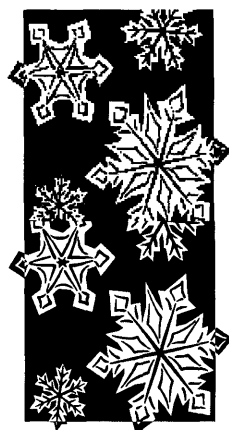
¹⁸⁵ For reviews of the Pictet-Spengler reaction, see: (a) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, 6, 151. (b) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, 95, 1797.



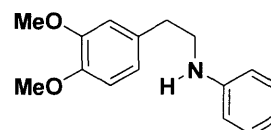
Scheme 30



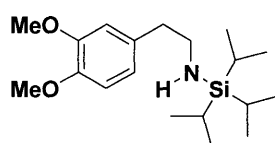
Leitner noted that certain amines formed visible white solids in the presence of CO_2 , which he attributed to the formation of carbamic acid or ammonium carbamate salts.¹⁷⁴ Similarly, we treated solutions of protected amines **422–425** in hexanes (0.5 M) with dry ice and looked for visual evidence of carbamic acid or ammonium carbamate salt formation. Amine **422** formed a white precipitate under these conditions, and this observation is in agreement with



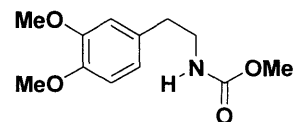
422 (white precipitate)



424 (no precipitate)



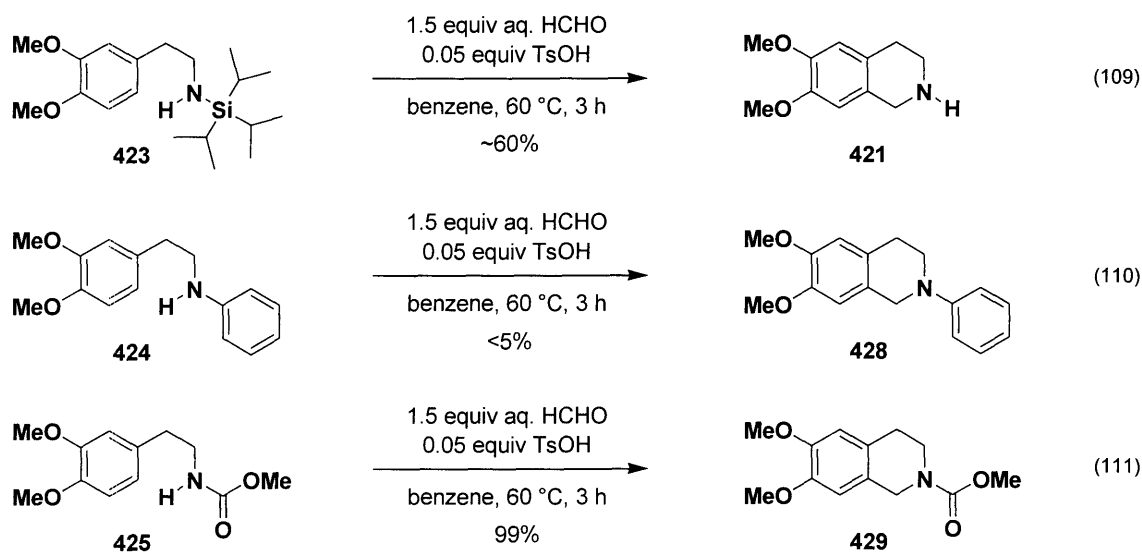
423 (no precipitate)



425 (no precipitate)

previous reports that benzyl groups do not suppress nucleophilic addition to CO₂.^{174,178c} No solids were formed when amines **423–425** were exposed to carbon dioxide, which is consistent with minimal carbamic acid or ammonium carbamate formation.

Before exploring Pictet-Spengler reactions with **423–425** in scCO₂, we first investigated these cyclizations using standard conditions in conventional solvents. The reaction of **423** with aqueous formaldehyde and acid led to deprotected tetrahydroisoquinoline **421** due to cleavage of the triisopropylsilyl group either before or after cyclization. Treatment of **424** under the same conditions led to decomposition via electrophilic additions of formaldehyde to the aniline ring. Carbamate **425**, however, participated in an “acyl-Pictet-Spengler reaction”¹⁸⁶ to afford **429** in near quantitative yield.



The reaction of amines protected as carbamates offered an appealing approach to Pictet-Spengler cyclizations in scCO₂. These substrates appeared inert to carbon dioxide, and so addition of **425** to aldehydes would not be impeded by the formation of carbamic acid or ammonium carbamate salts. In addition, the intermediate N-acyliminium ions are known to exhibit enhanced reactivity in Pictet-Spengler reactions.¹⁸⁷ Finally, several methods have been reported for the synthesis of carbamates from amines in scCO₂, and we were intrigued by the

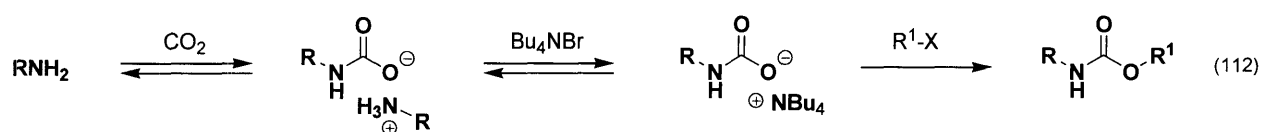
¹⁸⁶ For studies of acyl-Pictet-Spengler reactions in conventional solvent, see: (a) Venkov, A. P.; Lukanov, L. K. *Synth. Commun.* **1992**, 22, 3235. (b) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, 126, 10558. For an industrial application, see: (c) Dunn, P. J. *Org. Process Res. Dev.* **2005**, 9, 88.

¹⁸⁷ Reviewed in: Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, 104, 1431.

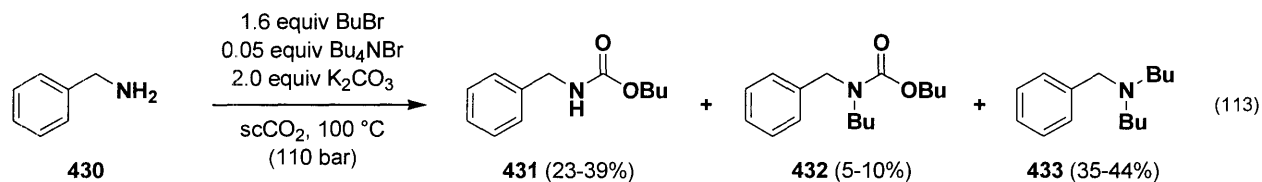
prospect of converting our amine substrates to carbamates in situ before subsequent Pictet-Spengler cyclization.

Protection of Amines as Carbamates in Supercritical Carbon Dioxide

In 2000, Yoshida reported the synthesis of carbamates from amines in scCO₂ via alkylation of ammonium carbamate salts with alkyl halides (eq 112).¹⁸⁸ This method employs a phase transfer catalyst which exchanges cations with the ammonium carbamate salt; the resulting



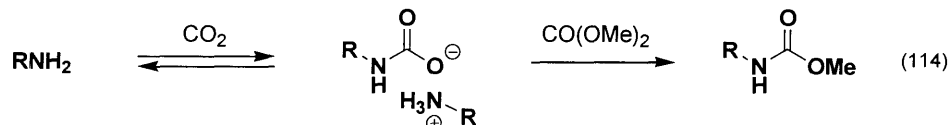
tetrabutylammonium carbamate species is more nucleophilic and reported to be soluble in scCO₂. Yoshida reported the synthesis of butyl carbamate **431** in 85% yield (eq 113); however, our attempts to reproduce his results using benzylamine as a test substrate afforded significant amounts of **432** and **433** as products from competitive N-alkylation. We speculate that our failure to reproduce Yoshida's protocol is due to mechanical difficulties associated with our reactor design, as the initial reaction of benzylamine with CO₂ formed a thick white precipitate that obstructed the stirring ability of the magnetic stirbar. Without proper mixing, it seems that portions of the amine were trapped beneath the precipitate and did not have suitable access to CO₂. As a result, the benzylamine reacted directly with butyl bromide in pathways leading to **432** and **433**.



The alkyl halides, phase transfer catalysts, and potassium carbonate employed by Yoshida were unattractive to us from an environmental point of view, and we turned our

¹⁸⁸ Yoshida, M.; Hara, N.; Okuyama, S. *Chem. Commun.* **2000**, 151.

attention instead to the use of dimethyl carbonate (DMC) as a “green methylating agent”¹⁸⁹ for the generation of methyl carbamates from amines in scCO₂ (eq 114).^{190,191} Two possible



mechanisms for this transformation are shown below. Reaction of the ammonium carbamate salt with DMC via an S_N2 pathway would directly provide the methyl carbamate with carbon dioxide and methanol as byproducts (eq 115).¹⁹⁰ Alternatively, addition of the ammonium carbamate salt to the carbonyl group of DMC could lead ultimately to the methyl carbamate via decarboxylation of the mixed carbamic-carbonic anhydride intermediate shown below (eq 116).¹⁹¹ The mode of reactivity of DMC as an electrophile is dependent on temperature;¹⁸⁹ above 100 °C the reagent behaves as a methylating agent, and we believed that under the conditions we envisioned using, DMC would react via the pathway of eq 115.

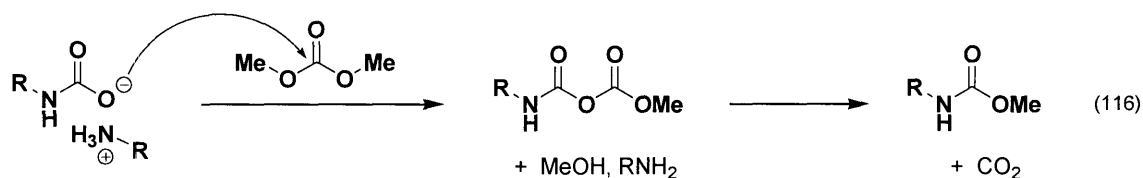
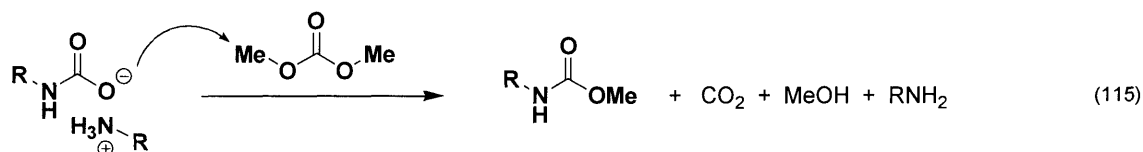


Table 10 summarizes the results of our optimization of conditions for the in situ generation of carbamates **425** and **434** from **420**. In a typical reaction, a biphasic system forms consisting of a lower density supercritical CO₂ phase and a higher density CO₂-rich liquid phase, the latter containing dialkyl carbonate and the ammonium carbamate salt derived from the

¹⁸⁹ Tundo, P.; Selva, M. *Acc. Chem. Res.* **2002**, *35*, 706.

¹⁹⁰ For an initial report on the conversion of amines to methyl carbamates with DMC in scCO₂, see: (a) Selva, M.; Tundo, P.; Perosa, A. *Tetrahedron Lett.* **2002**, *43*, 1217. For a detailed investigation of this reaction reported during the course of our studies, see: (b) Selva, M.; Tundo, P.; Perosa, A.; Dall'Acqua, F. *J. Org. Chem.* **2005**, *70*, 2771.

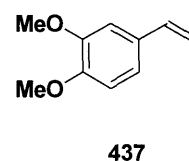
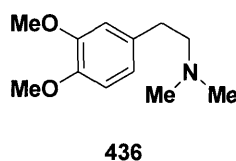
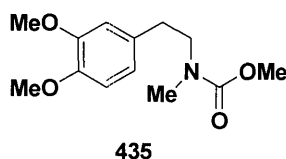
¹⁹¹ For an earlier report on the synthesis of methyl carbamates from amines, DMC, and gaseous CO₂, see: Aresta, M.; Quaranta, E. *Tetrahedron* **1991**, *47*, 9489.

Table 10. Synthesis of Carbamates in scCO₂ from Dialkyl Carbonates.

entry	carbonate (equiv) ^a	T (°C)	P (bar)	product	yield (%) ^b
1	DMC (1.1)	130	120-130	425	48
2	DMC (1.5)	130	120-130	425	62
3	DMC (2.0)	130	120-130	425	66
4	DMC (7.5)	130	120-130	425	77
5	DMC (1.5)	130	~1 ^c	425	47
6	DMC (1.5)	130	95-100	425	55
7	DMC (1.5)	130	180-190	425	55
8	DMC (2.0)	100	120-130	425	54 (77) ^d
9	DMC (2.0)	110	120-130	425	56 (62) ^e
10	DMC (2.0)	150	120-130	425	61
11	DBC (2.0)	130	120-130	434	69

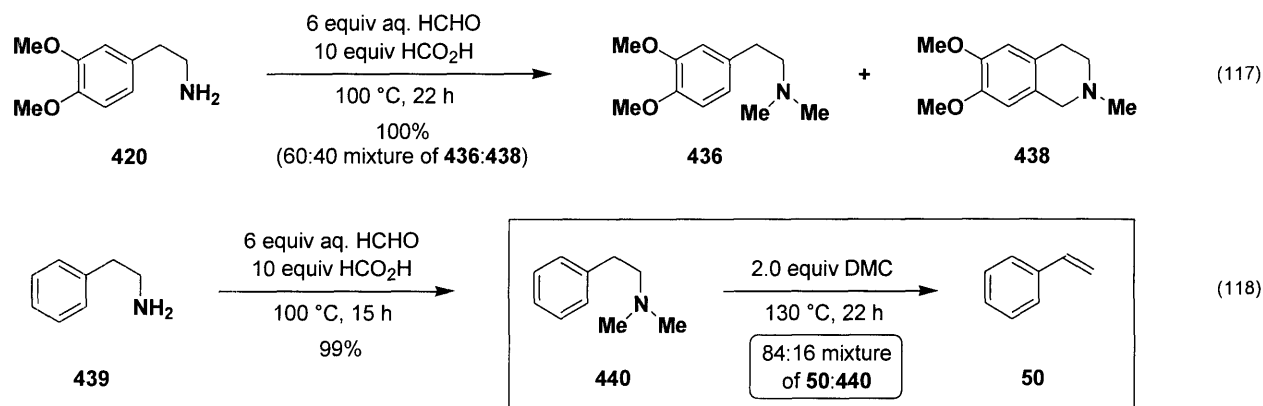
^a DMC = dimethyl carbonate, DBC = dibenzyl carbonate. ^b Isolated yields of products purified by column chromatography. ^c Reaction in a sealed glass tube under atmosphere of CO₂. ^d Corrected yield based on 75% conversion of **420**. ^e Corrected yield based on 90% conversion of **420**.

reaction of amine **420** with carbon dioxide. After 24 h at 130 °C, complete conversion of **420** was observed leading in quantitative yield to a mixture of carbamate **425** and the side products **435–437**. Thus, a critical issue was to maximize the alkylation of the intermediate carbamate salts (leading to the desired product) relative to the competing N-alkylation of the amine starting material (which was shown to be responsible for the formation of these side products).



We speculated that styrene **437** is generated via the N-methylation of tertiary amine **436** by DMC followed by elimination of trimethylamine. To test our hypothesis, we were interested

in preparing a sample of **436** that we could treat with DMC at the elevated temperature of our carbamate synthesis. Unfortunately, our attempts to methylate amine **420** using formaldehyde and formic acid led to the tertiary amine **436** and tetrahydroisoquinoline **438** as an inseparable mixture (eq 117). The formation of **438** via Pictet-Spengler cyclization is not surprising when considering the iminium ion intermediates generated in this reaction. Unable to isolate a pure sample of amine **436**, we instead turned our attention to the preparation of the analogous amine **440**, which we synthesized in near quantitative yield without competitive cyclization of iminium ion intermediates (eq 118). In the absence of CO₂, we heated a sample of amine **440** with 2 equiv of DMC at 130 °C and isolated an 84:16 mixture of styrene (**50**) and unreacted amine. This suggests that the analogous styrene **437** formed during the course of our carbamate synthesis is the result of N-methylation of tertiary amine **436** by DMC and subsequent elimination of trimethylamine.



As previously explained, the key issue in optimizing conditions for our carbamate synthesis (Table 10) was to promote the methylation of intermediate carbamate salts (leading to desired product) over competitive N-alkylation of the amine starting material (leading to **435**–**437**). The equilibrium formulated in eq 114 (see page 109) should be shifted further toward the ammonium carbamate with an increase in the concentration of carbon dioxide in the CO₂-expanded liquid phase, leading to an increase in the selectivity for alkylation of carbamate salt over amine. Dimethyl carbonate readily absorbs carbon dioxide,¹⁹² and so an increase in the amount of DMC employed results in an increase in the amount of CO₂ in the liquid

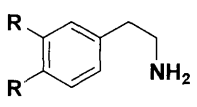
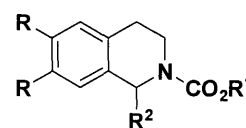
¹⁹² (a) Im, J.; Kim, M.; Lee, J.; Kim, H. *J. Chem. Eng. Data* **2004**, *49*, 243. (b) Camy, S.; Pic, J.-S.; Badens, E.; Condoret, J.-S. *J. Supercrit. Fluid* **2003**, *25*, 19.

DMC/ammonium carbamate salt phase. This leads to an increase in selectivity for the desired alkylation, and thus an improved yield of **425** (Table 10, entries 1–4). The concentration of methanol byproduct, which has been shown to lower the selectivity for carbamate formation,^{190b} is also reduced in the presence of more DMC. Improved yields of **425** are also observed with increasing CO₂ pressure, which similarly promotes carbamate salt formation via an increase in liquid phase CO₂ concentration¹⁹² (compare entries 2, 5, and 6). It is noteworthy that the selectivity for **425** decreases at very high pressures (entry 7) where DMC partitions from the liquid phase into the blanket scCO₂ phase, resulting in a smaller volume of DMC in the liquid phase (verified visually), and thus a lower concentration of carbon dioxide in this phase. Selectivity for **425** over **435–437** increases at lower temperatures (entry 8), possibly due to (a) increased absorption of carbon dioxide into the liquid phase at lower temperatures,¹⁹² and/or (b) slower N-methylation of the amine at temperatures ≤ 100 °C.¹⁸⁹ However, alkylation of the ammonium carbamate salt is also sluggish at 100 °C resulting in incomplete conversion after 24 h. Finally, this strategy for the in situ protection of amines in scCO₂ can also be extended to the formation of benzyl carbamates such as **434** by substituting dibenzyl carbonate (DBC) for DMC (entry 11). The utility of Cbz derivatives as protective groups for amines is well-established.

Acyl-Pictet-Spengler Cyclizations in Supercritical CO₂/CO₂-Expanded Liquid Media

We next turned our attention to examining the use of the in situ generated carbamates as substrates for acyl-Pictet-Spengler reactions in a triphasic system consisting of a scCO₂ phase, a CO₂-rich liquid phase, and a H₂O-rich liquid phase. Table 11 delineates the scope of this two-stage strategy for effecting acyl-Pictet-Spengler reactions of β -arylethylamines. Typical conditions involve treating the amine with dialkyl carbonate in scCO₂ at 130 °C (120–130 bar) for 24 h, cooling the resulting reaction mixture to 80 °C, and then adding the aldehyde and acid (1.5 equiv) via a pressurized injection loop. Further reaction at 80 °C for 24 h then affords the desired tetrahydroisoquinolines. Both electron-neutral and electron-rich β -arylethylamines participate in the reaction, which can also be applied to a variety of aliphatic and aromatic aldehydes. Acyl-Pictet-Spengler reaction with methyl glyoxylate can be achieved by introducing this aldehyde in the form of its dimethyl acetal derivative. Trifluoroacetic acid can be employed

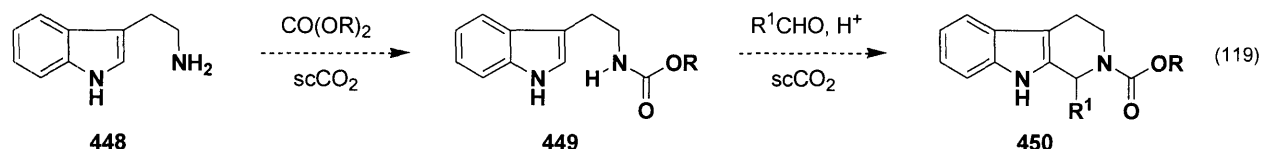
Table 11. Two-Stage Synthesis of Tetrahydroisoquinolines

<div style="display: flex; align-items: center; justify-content: center;"> <div style="text-align: center;">  <p>439 (R = H) 420 (R = OMe)</p> </div> <div style="margin: 0 20px; text-align: center;"> $\xrightarrow[\text{then inject}]{\text{CO(OR}^1\text{)}_2, \text{scCO}_2}$ <p>130 °C, 24 h (120-130 bar)</p> <p>1.5 equiv R²CHO 1.5 equiv acid scCO₂, 80 °C, 24 h (140-160 bar)</p> </div> <div style="text-align: center;">  <p>429, 441-447</p> </div> </div>						
entry	amine	carbonate R ¹ (equiv)	R ²	acid ^a	product	yield (%) ^b
1	439	Me (2.0)	H	H ₂ SO ₄	441	52
2	420	Me (2.0)	H	H ₂ SO ₄	429	54
3	420	Me (2.0)	H	TFA	429	62
4	420	Me (7.5)	H	H ₂ SO ₄	429	63
5	420	Me (2.0)	Ph	H ₂ SO ₄	442	56
6	420	Me (7.5)	Ph	H ₂ SO ₄	442	69
7	420	Me (2.0)	<i>i</i> -Pr	H ₂ SO ₄	443	53
8	420	Me (7.5)	<i>i</i> -Pr	H ₂ SO ₄	443	71
9	420	Me (2.0)	CO ₂ Me ^c	H ₂ SO ₄	444	49
10	420	Bn (2.0)	H	TFA	445	67
11	420	Bn (2.0)	Et	TFA	446	71
12	420	Bn (2.0)	Ph	H ₂ SO ₄	447	57

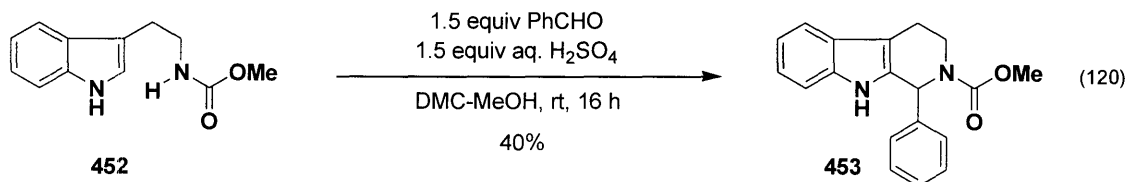
^a 9.0 M H₂SO₄ or 50% v/v TFA in H₂O. ^b Isolated yields of products purified by column chromatography. ^c Reaction with (MeO)₂CHCO₂Me as methyl glyoxylate equivalent.

in place of the “greener” H₂SO₄ to promote iminium ion formation, and its use leads to somewhat improved yields due to the sensitivity of some carbamate groups to sulfuric acid under these conditions. It is particularly noteworthy that benzyl carbamates are compatible with H₂SO₄ in the presence of carbon dioxide (entry 12), as our attempts to perform acyl-Pictet-Spengler cyclizations with benzyl carbamates under similar conditions but without CO₂ led to cleavage of the Cbz group. Thus, it appears that carbon dioxide acts as a buffer for strong acids such as H₂SO₄. Finally, we observed that the overall yield for this two-stage process improves somewhat as the volume of DMC increases from 2.0 to 7.5 equiv relative to the amine. This effect is attributed to improved selectivity for carbamate formation over N-methylation (vide supra).

We next were interested in extending the scope of our acyl-Pictet-Spengler reactions in multiphasic $\text{scCO}_2/\text{CO}_2$ -expanded liquid media to include the synthesis of tetrahydro- β -carbolines (eq 119). The reaction of tryptamine (**448**) with dialkyl carbonate in scCO_2 would protect the aliphatic amine as a carbamate derivative, and we expected that the nitrogen atom embedded within the indole would not react with carbon dioxide and DMC under these conditions.¹⁹³ After the in situ formation of carbamate **449**, we anticipated that treatment with aldehyde and acid would furnish tetrahydro- β -carbolines of type **450**.



While the reaction of tryptamines in Pictet-Spengler cyclizations is well-documented,^{185b} the literature contains only scattered examples of the *acyl*-Pictet-Spengler variant proposed in eq 119.¹⁹⁴ We suspected that the electron-withdrawing group on the aliphatic amine might diminish its nucleophilicity to the extent that electrophilic addition of the aldehyde to the electron-rich indole ring becomes a competitive process. To test the feasibility of using our tryptamine substrates in acyl-Pictet-Spengler cyclizations, we prepared a sample of **451** and exposed it to various aldehydes in the presence of acid (no CO_2 present). Although we were able to isolate tetrahydro- β -carboline **452** in modest yield after treating **451** with benzaldehyde as shown below, the reaction of **451** with other aldehydes (e.g., HCHO , $i\text{-PrCHO}$) in the presence of H_2SO_4 or TFA provided the desired tetrahydro- β -carbolines in poor yield and led to the formation of various side products via electrophilic addition of the aldehydes to the indole ring.

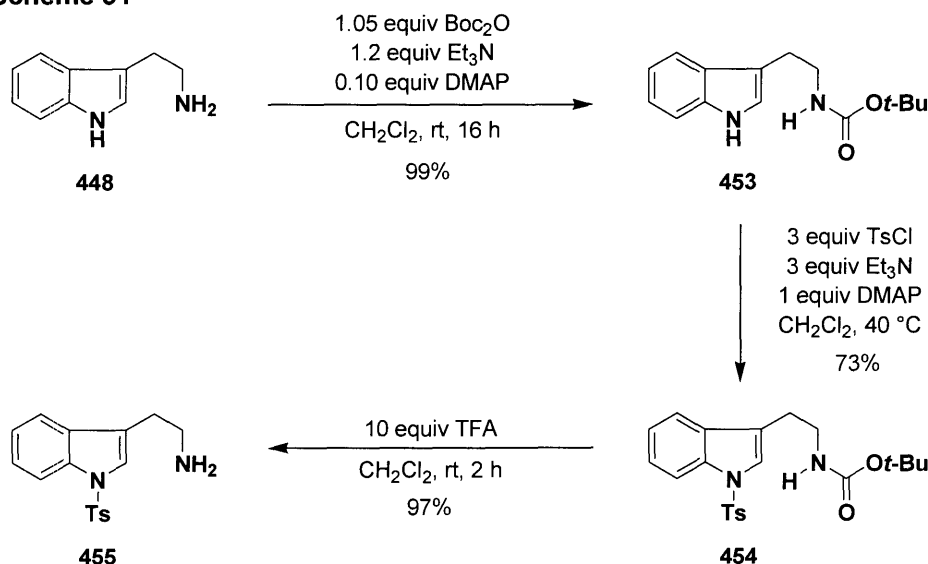


¹⁹³ Less nucleophilic amines (i.e., anilines) do not participate in the carbamate synthesis. See ref 190b.

¹⁹⁴ For examples, see: (a) Lögers, M.; Overman, L. E.; Welmaker, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 9139. (b) Madalengoitia, J. S.; Tepe, J. J.; Werbovetz, K. A.; Lehnert, E. K.; Macdonald, T. L. *Bioorg. Med. Chem.* **1997**, *5*, 1807. (c) Gremmen, C.; Willemse, B.; Wanner, M. J.; Koomen, G.-J. *Org. Lett.* **2000**, *2*, 1955. (d) Tsuji, R.; Nakagawa, M.; Nishida, A. *Tetrahedron: Asymmetry* **2003**, *14*, 177. (e) Revell, J. D.; Srinivasan, N.; Ganesan, A. *Synlett* **2005**, 1428.

We thought to reduce the nucleophilicity of the indole by installing an electron-withdrawing group on the heterocycle, and we turned our attention to the preparation of deactivated tryptamine **455**¹⁹⁵ (Scheme 31). This was accomplished in three steps from the parent tryptamine (**448**). The aliphatic amine was protected as the Boc carbamate **453** and then tosylation of the indole provided sulfonamide **454**. The sulfonylation of the heterocycle was surprisingly sluggish and required several days to proceed to completion after repeated additions of tosyl chloride, triethylamine, and DMAP to the reaction mixture. Finally, cleavage of the Boc carbamate provided **455** for our acyl-Pictet-Spengler cyclization studies in scCO₂.

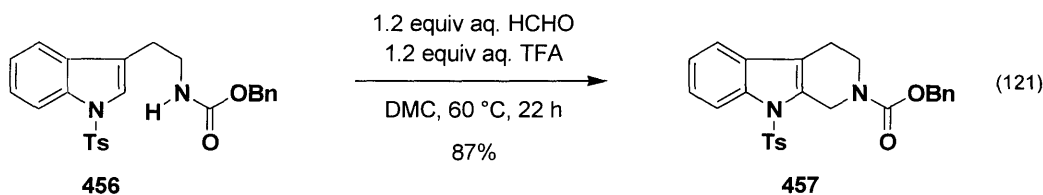
Scheme 31



Before investigating the in situ generation of the carbamate derivative of **455** and its acyl-Pictet-Spengler cyclization, we first explored the facility of the proposed acyl-Pictet-Spengler reaction. We were pleased to find that the reaction of benzyl carbamate **456**¹⁹⁶ under the conditions shown in eq 121 afforded tetrahydro- β -carboline **457** in excellent yield. In addition, we did not detect any side products from undesired electrophilic addition of formaldehyde to the indole. We then explored deactivated tryptamine **455** as a substrate for acyl-Pictet-Spengler

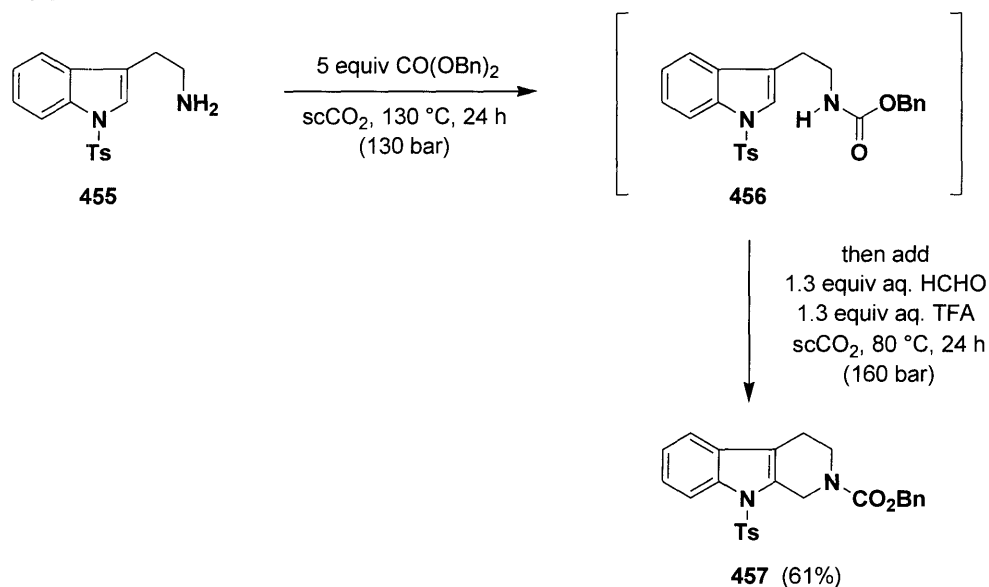
¹⁹⁵ For previous syntheses of **455** by different routes, see: Grieco, P. A.; Clark, J. D. *J. Org. Chem.* **1990**, *55*, 2271 and ref 194a.

¹⁹⁶ A sample of **456** was prepared by tosylation of the corresponding indole (e.g. KHMDS, TsCl). A sample of the indole precursor was available from earlier studies on the conversion of tryptamine (**448**) to its benzyl carbamate derivative via reaction with DBC in scCO₂.



cyclization in multiphasic $\text{scCO}_2/\text{CO}_2$ -expanded media, and the application of our protocol to tryptamine **455** provides tetrahydro- β -carboline **457** in good yield over two steps (Scheme 32).

Scheme 32



Summary

We have developed conditions to effect acyl-Pictet-Spengler reactions in multiphasic $\text{scCO}_2/\text{CO}_2$ -expanded liquid media.¹⁹⁷ Critical to the success of these reactions is the in situ conversion of β -arylethylamine reactants to carbamate derivatives by reaction with CO_2 and dialkyl carbonates. The application of this general strategy for utilizing amines in other carbon-nitrogen bond-forming reactions in environmentally-friendly media is under investigation.

¹⁹⁷ This work has appeared in a communication: Dunetz, J. R.; Ciccolini, R. P.; Fröling, M.; Paap, S. M.; Allen, A. J.; Holmes, A. B.; Tester, J. W.; Danheiser, R. L. *Chem. Commun.* **2005**, 4465.

Part III

Experimental Section

Experimental Section for Part I

General Procedures. All reactions were performed in flame-dried or oven-dried glassware under a positive pressure of argon. Reaction mixtures were stirred magnetically unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred by syringe or cannula and introduced into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated by rotary evaporation at ca. 20 mmHg and then at ca. 0.1 mmHg (vacuum pump) unless otherwise indicated. Thin layer chromatography was performed on Merck precoated glass-backed silica gel 60 F-254 0.25 mm plates. Column chromatography was performed on EM Science silica gel 60 or Silicycle silica gel 60 (230-400 mesh).

Materials. Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane and tetrahydrofuran were purified by pressure filtration through activated alumina. Toluene was purified by pressure filtration through activated alumina and Cu(II) oxide. Pyridine was distilled under argon from calcium hydride. Piperidine, triethylamine, and hexamethyldisilazane were distilled under argon from calcium hydride. Chlorotrimethylsilane, chlorotriisopropylsilane, (trifluoromethanesulfonyl)-triisopropylsilane, and trifluoromethanesulfonyl anhydride were distilled under argon from phosphorous pentoxide. Methyl chloroformate was distilled under argon. Copper(I) iodide was extracted with THF for 24 h in a Soxhlet extractor and then dried under vacuum (0.1 mmHg). Palladium(II) chloride (bis)triphenylphosphine was recrystallized from boiling chloroform. *N*-Bromosuccinimide was recrystallized from boiling water. 2-Bromopropene was passed through a pad of alumina in a disposable pipette prior to use.

Preparation of 1-Haloacetylenes. All of the 1-haloacetylenes from Part I are previously known compounds with the exception of bromo diynes **249** and **254**. We used the general method of Hofmeister (NBS, cat. AgNO₃)¹¹⁷ to prepare bromo alkynes **224–232** from the corresponding terminal acetylenes.¹⁹⁸ Iodo alkynes **237**¹⁹⁹ and **238**,²⁰⁰ and bromo alkynes **234**,¹¹⁸ **241**,¹¹⁹ and **242**¹²⁰ were prepared according to the literature procedure. We used the general method of Hansen (*n*-BuLi, TsCl)¹²¹ to prepare chloro alkyne **243**.²⁰¹ Our syntheses of previously unknown bromo diynes **249** and **254** are reported in this experimental section. *Caution: 1-Haloacetylenes are strong lachrymators!*

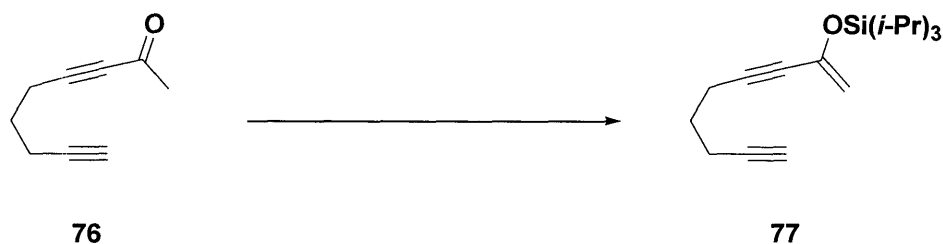
Instrumentation. Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained using a Perkin Elmer 2000 FT-IR spectrophotometer. ¹H NMR and ¹³C NMR spectra were measured with an Inova 500 spectrometer. ¹H NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the CHCl₃ peak at 7.27 ppm used as a standard). ¹³C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the central peak of CHCl₃ at 77.23 ppm used as a standard). Low resolution mass spectra (GC-MS) were measured on a Agilent 6890N series gas chromatograph with Agilent 5973 series mass selective detection. High resolution mass spectra (HRMS) were measured on a Bruker Daltonics APEXII 3 Tesla Fourier transform mass spectrometer. Elemental analyses were performed by E&R Microanalytical Laboratory, Inc. of Parsippany, NJ.

¹⁹⁸ For previous syntheses of these bromo alkynes: (a) **224**: Li, L.-S.; Wu, Y.-L. *Tetrahedron Lett.* **2002**, 43, 2427. (b) **225**: Cai, C.; Vasella, A. *Helv. Chim. Acta* **1995**, 78, 2053. (c) **226**: Leroy, J. *Synth. Commun.* **1992**, 22, 567. (d) **227**: Chen, C.; Crich, D.; *J. Chem. Soc., Chem. Commun.* **1991**, 1289. (e) **228**: Rubin, Y.; Lin, S.-S.; Knobler, C. B.; Anthony, J.; Boldi, A. M.; Diederich, F. *J. Am. Chem. Soc.* **1991**, 113, 6943. (f) **229**: Stefani, H. A.; Menezes, P. H.; Costa, I. M.; Silva, D. O.; Petragani, N. *Synlett* **2002**, 1335. (g) **230**: Shoup, T. M.; Zweifel, G. *Synth. Commun.* **1993**, 23, 2937. (h) **231**: Petrov, A. A. *Chem. Abstr.* **1944**, 1466. (i) **232**: Crombie, A. L. Ph. D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, June 2004.

¹⁹⁹ Luithle, J. E. A.; Pietruszka, J.; *Eur. J. Org. Chem.* **2000**, 14, 2557.

²⁰⁰ Siegel, K.; Brueckner, R. *Synlett* **1999**, 1227.

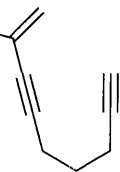
²⁰¹ For a previous synthesis of chloro alkyne **243**, see: Martins, M. A. P.; Emmerich, D. J.; Pereira, C. M. P.; Cunico, W.; Rossato, M.; Zanatta, N.; Bonaccorso, H. G. *Tetrahedron Lett.* **2004**, 45, 4935.



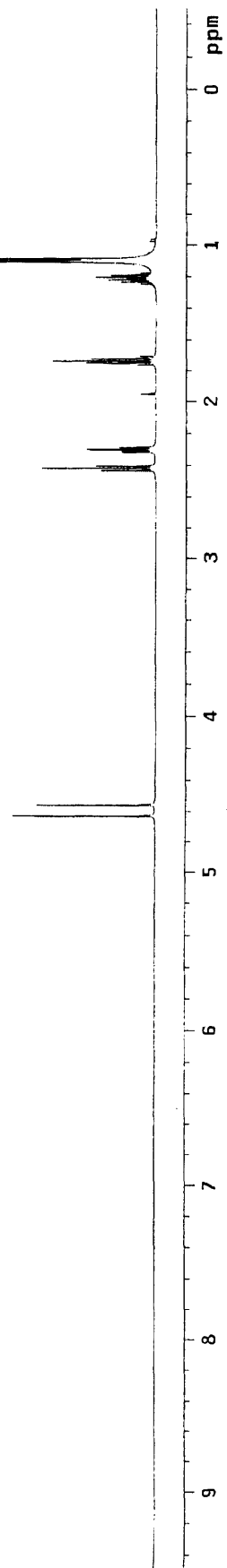
2-(Triisopropylsiloxy)-1-nonen-3,8-diyne (**77**).

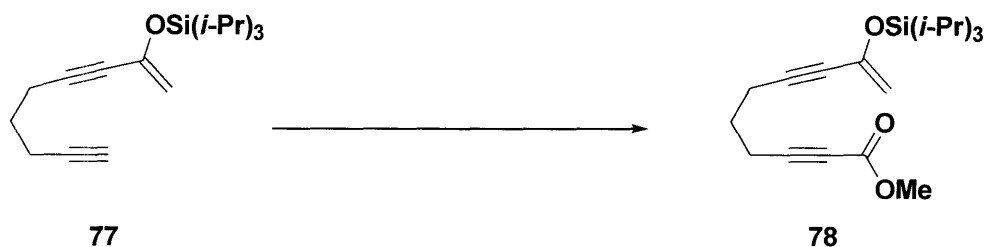
A 25-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with ketone **76** (0.231 g, 1.72 mmol) and 5.7 mL of CH₂Cl₂. The solution was cooled at 0 °C while triethylamine (0.36 mL, 0.26 g, 2.6 mmol) was added via syringe in one portion. Triisopropylsilyl triflate (0.56 mL, 0.64 g, 2.1 mmol) was added via syringe over 30 sec, the ice bath was removed, and the resulting solution was stirred at rt for 4 h. The reaction mixture was diluted with 20 mL of CH₂Cl₂ and washed with 10 mL of water. The aqueous phase was extracted with 10 mL of CH₂Cl₂, and the combined organic phases were washed with 20 mL of satd NaCl solution, dried over MgSO₄, filtered, and concentrated to provide 0.608 g of a colorless oil with red precipitate. Column chromatography on 30 g acetone-deactivated silica gel (elution with hexanes) provided 0.465 g (93%) silyl enol ether **77** as a colorless oil: IR (neat) 3312, 2945, 2867, 2229, 2120, 1604, 1464, and 1283 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.63 (s, 1H), 4.56 (s, 1H), 2.42 (t, *J* = 7.0 Hz, 2H), 2.30 (dt, *J* = 2.7, 7.0 Hz, 2H), 1.95 (t, *J* = 2.7 Hz, 1H), 1.74 (app quint, *J* = 7.0 Hz, 2H), 1.21 (sept, *J* = 3.7 Hz, 3H), and 1.10 (d, *J* = 3.7 Hz, 18H); ¹³C NMR (125 MHz, CDCl₃) δ 140.1, 101.4, 86.9, 83.4, 79.4, 69.1, 27.4, 18.2, 18.0, 17.7, and 12.8; HRMS-ESI *m/z*: [M+H]⁺ calcd for C₁₈H₃₀OSi, 291.2139; found, 291.2141.

OSi(*i*-Pr)₃



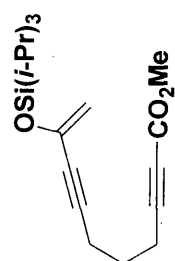
77



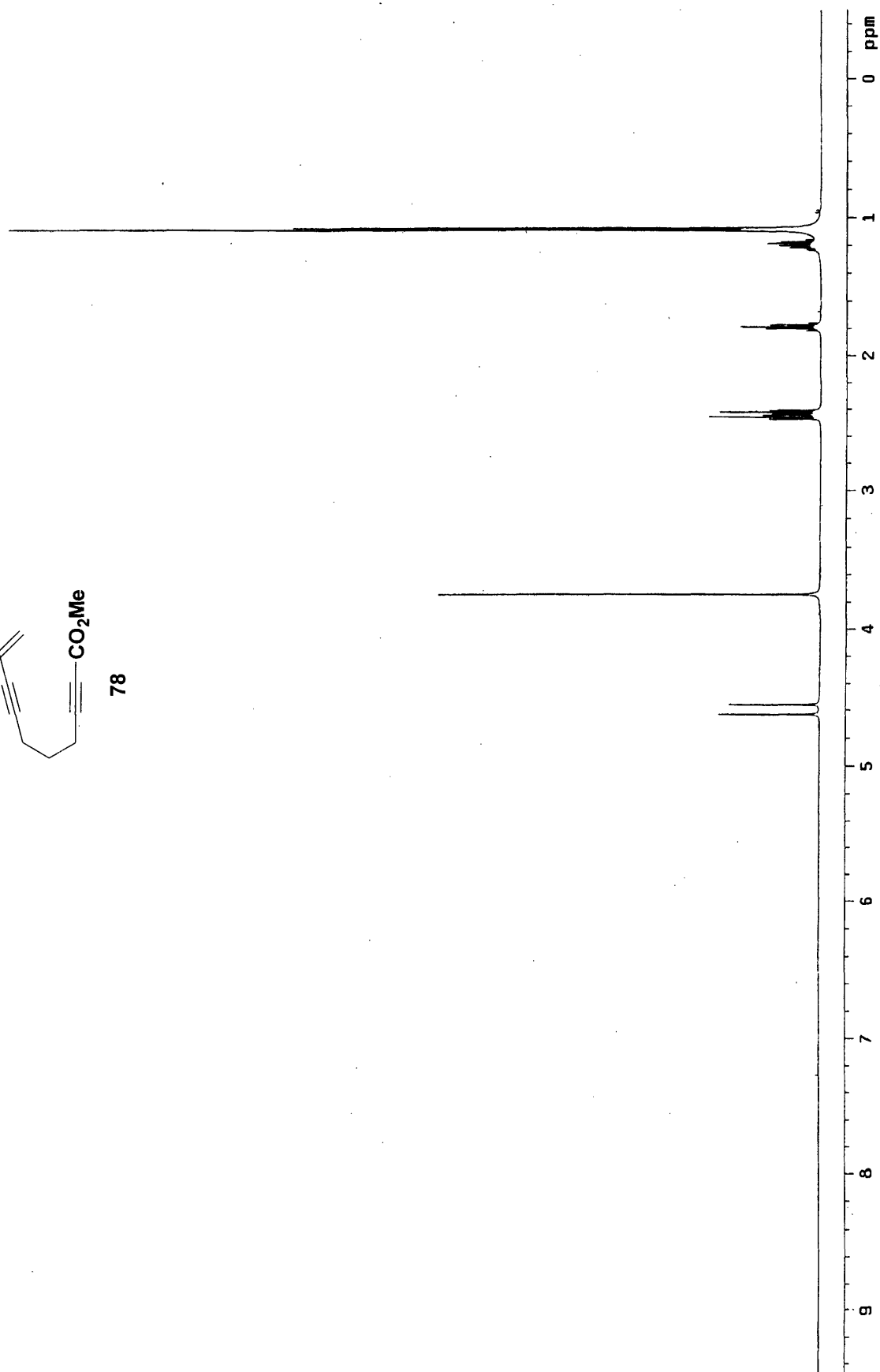


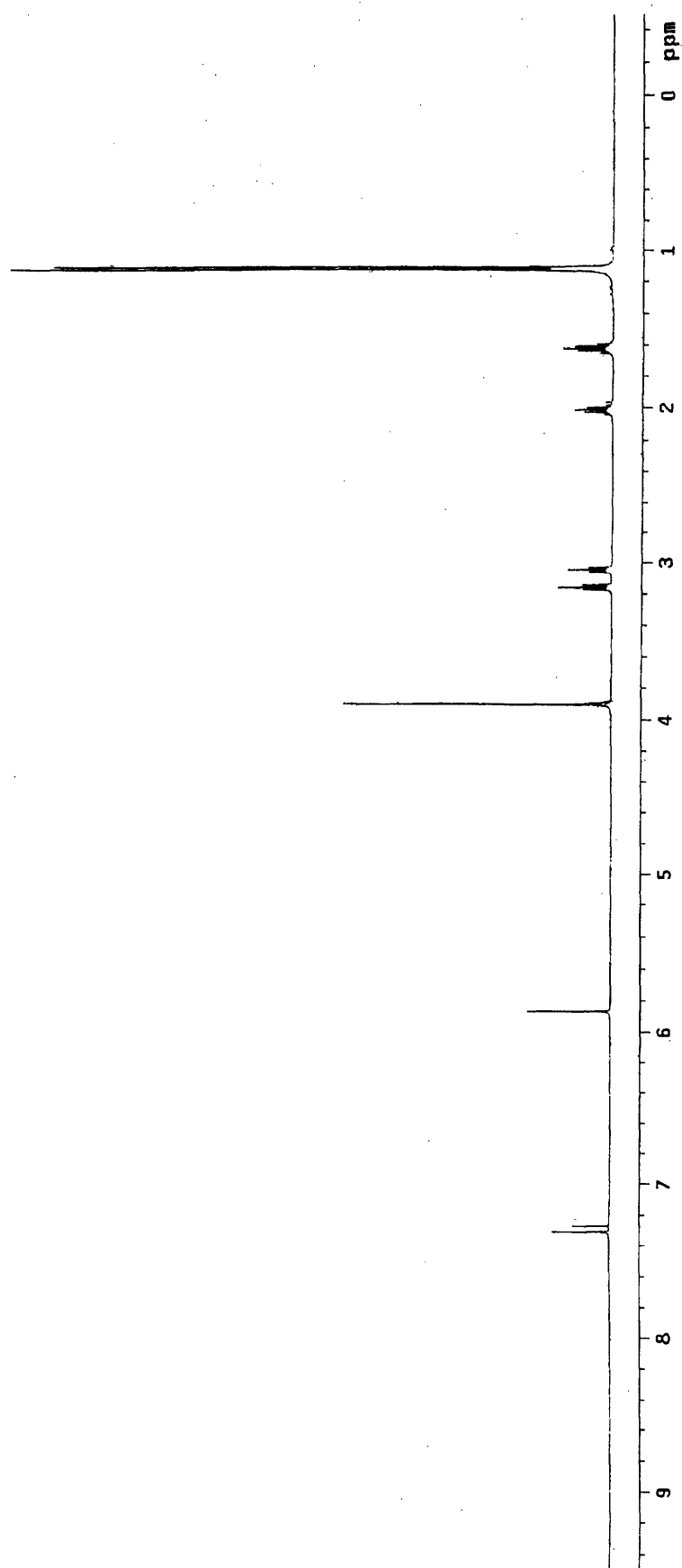
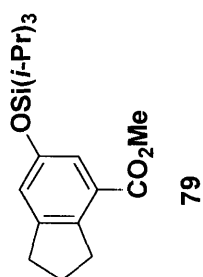
Methyl 9-(triisopropylsiloxy)-9-decen-2,7-diynoate (78).

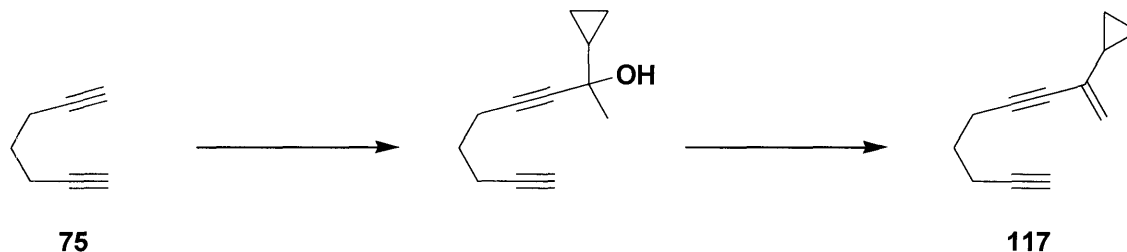
A 10-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with hexamethyldisilazane (0.20 mL, 0.15 g, 0.95 mmol) and 0.9 mL of THF. The solution was cooled to 0 °C while 0.37 mL of *n*-BuLi solution (2.39 M in hexanes, 0.88 mmol) was added via syringe over 20 sec. The ice bath was removed and the resulting solution was stirred at rt for 30 min. A 25-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with alkyne **77** (0.198 g, 0.682 mmol) and 6.8 mL of THF. The solution was cooled at –78 °C while the LiHMDS solution prepared as described above was added via cannula over 30 sec (two 0.5-mL THF rinses). The pale yellow solution was stirred at –78 °C for 2 h. Methyl chloroformate (0.53 mL, 0.65 g, 6.9 mmol) was added in one portion via syringe, and the resulting yellow reaction mixture was stirred at –78 °C for 3 h. The dry ice-acetone bath was replaced with an ice bath, and the reaction mixture was stirred at 0 °C for 2 h and then diluted with 30 mL of Et₂O. The solution was extracted with 30 mL of a 2:1 mixture of conc NH₄OH and satd NaCl solution, and the aqueous layer was extracted with two 10-mL portions of Et₂O. The combined organic layers were washed with 30 mL of satd NaCl solution, dried over MgSO₄, filtered, and concentrated to provide 0.378 g of a yellow solid. Column chromatography on 20 g acetone-deactivated silica gel (gradient elution with 0–2% EtOAc-hexanes) provided 0.110 g (46%) alkynyl ester **78** as a colorless oil: IR (neat) 2946, 2867, 2237, 1720, and 1604 cm^{–1}; ¹H NMR (500 MHz, CDCl₃) δ 4.63 (s, 1H), 4.56 (s, 1H), 3.74 (s, 3H), 2.46 (t, *J* = 7.0 Hz, 2H), 2.42 (t, *J* = 7.0 Hz, 2H), 1.79 (app quint, *J* = 7.0 Hz, 2H), 1.19 (sept, *J* = 7.0 Hz, 3H), and 1.08 (d, *J* = 7.0 Hz, 18H); ¹³C NMR (125 MHz, CDCl₃) δ 154.2, 140.0, 101.7, 88.4, 86.1, 79.8, 73.6, 52.7, 26.4, 18.4, 18.0, 17.9, and 12.7; HRMS-ESI *m/z*: [M+H]⁺ calcd for C₂₀H₃₂O₃Si, 349.2193; found, 349.2197.



78



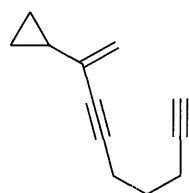




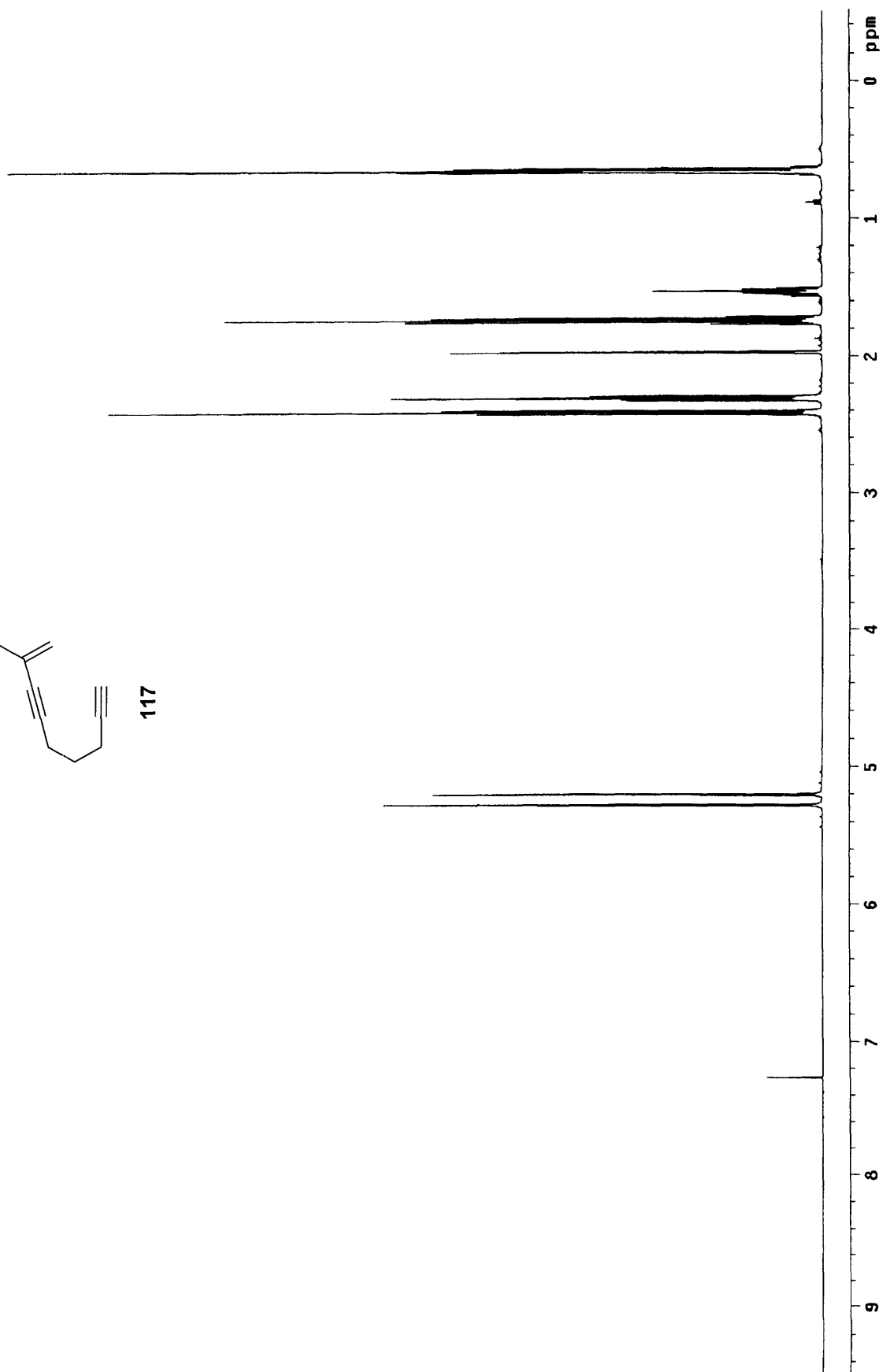
2-Cyclopropyl-1-nonen-3,8-diyne (117). A 1-L, three-necked, round-bottomed flask equipped with two rubber septa and an argon inlet adapter was charged with hepta-1,6-diyne (**75**) (5.00 g, 54.0 mmol) and 360 mL of THF and then cooled at 0 °C while 17.8 mL of ethylmagnesium bromide solution (3.04 M in diethyl ether, 54.0 mmol) was added dropwise via syringe over 15 min. After 2.5 h, a solution of cyclopropyl methyl ketone (18.3 g, 217 mmol) in 12 mL of THF was added dropwise over 15 min via cannula. The reaction mixture was allowed to warm to 15 °C, stirred for 13.5 h, and then diluted with 50 mL of satd NH₄Cl solution and 200 mL of water. The aqueous layer was separated and extracted with two 200-mL portions of *t*-butyl methyl ether, and the combined organic phases were concentrated to a volume of ca. 100 mL and washed with 300 mL of satd NaCl solution, dried over MgSO₄, filtered, and concentrated to provide 12.6 g of yellow oil. Purification by column chromatography on 500 g of silica gel (elution with 30% EtOAc-hexanes) gave 8.59 g of tertiary alcohol as a colorless oil that was used in the next step without further purification.

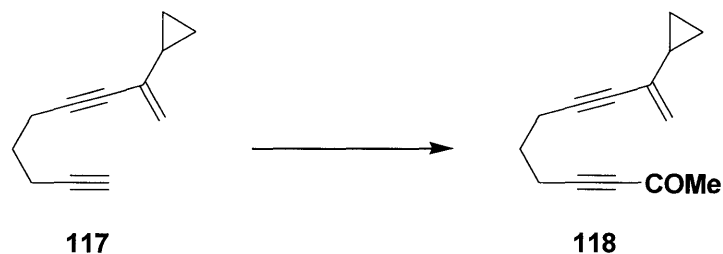
A 500-mL one-necked, round-bottomed flask equipped with a rubber septum and a argon inlet needle was charged with a solution of 4.30 g of the tertiary alcohol in 280 mL of CH₂Cl₂ and cooled at 0 °C while triethylamine (25.4 g, 251 mmol) and methanesulfonyl chloride (13.4 g, 116 mmol) were added sequentially via syringe over 5 min. After 1.75 h, the reaction mixture was diluted with 300 mL of satd NaCl solution and the aqueous layer was separated and extracted with two 200-mL portions of chloroform. The combined organic phases were dried over MgSO₄, filtered, and concentrated to provide 9.54 g of red oil containing some yellow solid. Column chromatography on 200 g of silica gel (elution with pentane) afforded 1.95 g (38%, overall from **75**) of enyne **117** as a colorless oil: IR (film) 3300, 3080, 3010, 2200, 2110, and 1595 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.28 (d, *J* = 1.7 Hz, 1H), 5.20 (d, *J* = 1.7 Hz, 1H), 2.41 (t, *J* = 7.0 Hz, 2H), 2.31 (dt, *J* = 7.0, 2.6 Hz, 2H), 1.97 (t, *J* = 2.6 Hz, 1H), 1.74 (quintet, *J* = 7.0 Hz, 2H), 1.50–1.57 (m, 1H), and 0.63–0.68 (m, 4H); ¹³C NMR (125 MHz,

CDCl_3) δ 134.3, 118.0, 89.2, 83.6, 78.4, 69.1, 27.8, 18.4, 17.7, 16.7, and 5.9; GC-MS m/z : 158 (M^+).

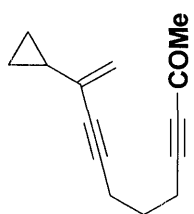


117

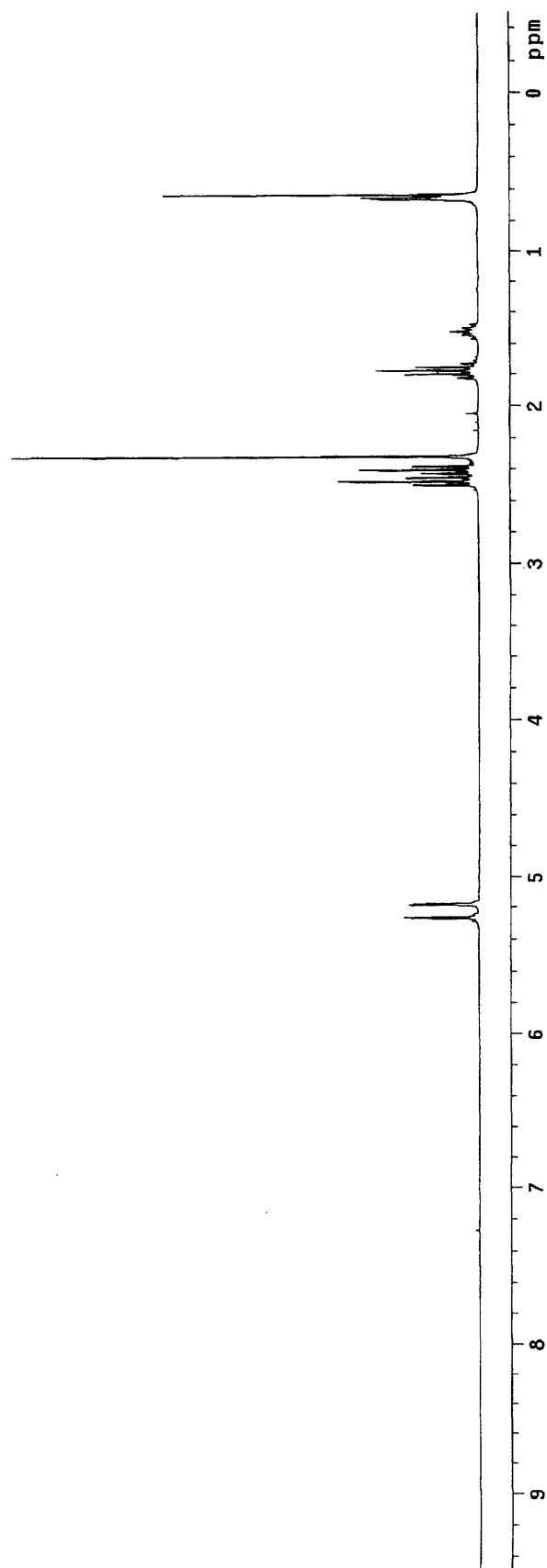


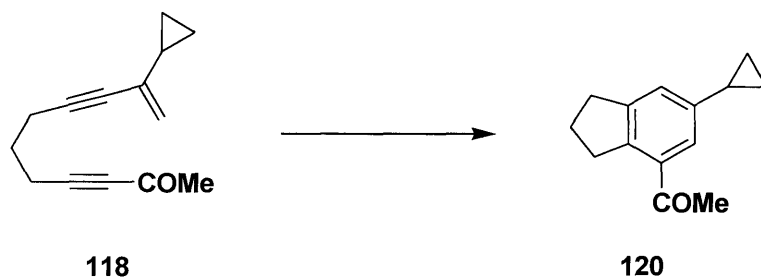


10-Cyclopropyl-10-undecen-3,8-diyn-2-one (118). A 100-mL, three-necked, round-bottomed flask equipped with two rubber septa and an argon inlet adapter was charged with 2-cyclopropyl-1-nonen-3,8-diyn-2-ol (**117**) (0.910 g, 5.75 mmol) and 48 mL of THF, and cooled at $-40\text{ }^{\circ}\text{C}$ while 2.5 mL of *n*-BuLi solution (2.51 M in hexane, 6.30 mmol) was added dropwise over 3 min. The resulting solution was stirred at $-50\text{ }^{\circ}\text{C}$ for 45 min. A 100-mL, three-necked, round-bottomed flask equipped with two rubber septa and an argon inlet adapter was charged with acetic anhydride (0.76 mL, 0.82 g, 8.1 mmol) and 6 mL of THF and then cooled at $-50\text{ }^{\circ}\text{C}$ while the solution of lithium acetylide was added via cannula over 4 min (4-mL THF rinse). The resulting mixture was allowed to warm to rt over 8 h and then cooled at $-50\text{ }^{\circ}\text{C}$ while 10 mL of satd NH_4Cl and 1 mL of satd NH_4OH solutions were added. The resulting solution was allowed to warm to rt and then diluted with 50 mL of satd NaCl solution. The aqueous phase was separated and extracted with three 50-mL portions of diethyl ether and the combined organic phases were washed with 50 mL of satd NaCl solution, dried over MgSO_4 , filtered, and concentrated to furnish 1.20 g of yellow oil. Column chromatography on 72 g of silica gel (elution with 3% EtOAc-hexanes) yielded 0.815 g (71%) of **118** as a yellow oil: IR (film) 3075, 3000, 2930, 2210, 1665, 1420, and 1350 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.25 (d, $J = 1.7\text{ Hz}$, 1H), 5.17 (d, $J = 1.7\text{ Hz}$, 1H), 2.46 (t, $J = 7.0$, 2H), 2.39 (t, $J = 7.0$, 2H), 2.30 (s, 3H), 1.77 (quintet, $J = 7.0\text{ Hz}$, 2H), 1.52 (m, 1H), and 0.63–0.66 (m, 4H); ^{13}C NMR (125 MHz, CDCl_3) δ 185.0, 134.1, 118.3, 92.8, 88.5, 81.9, 78.9, 33.0, 27.0, 19.5, 18.2, 16.7, and 5.9; GC-MS m/z : 200 (M^+).



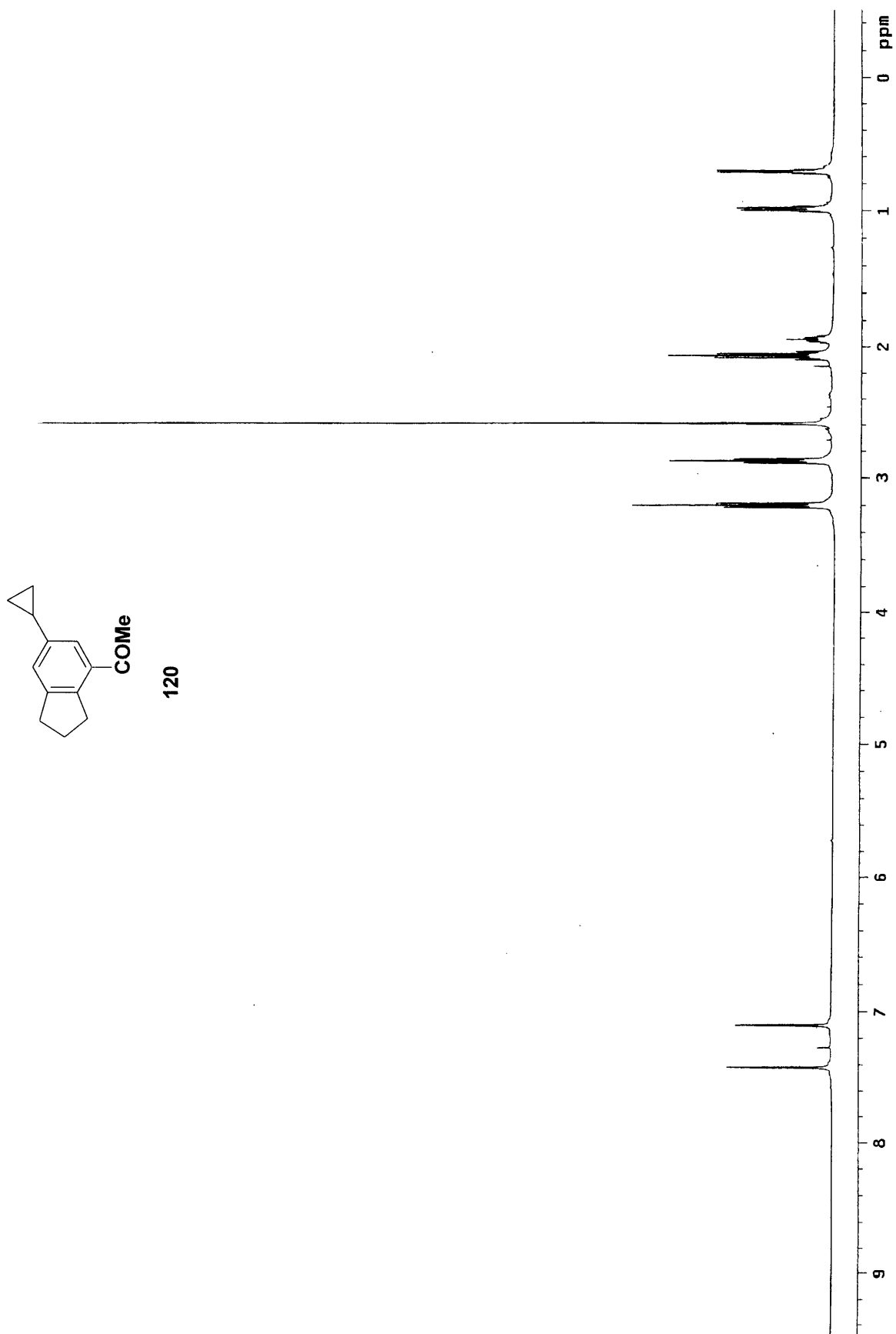
118





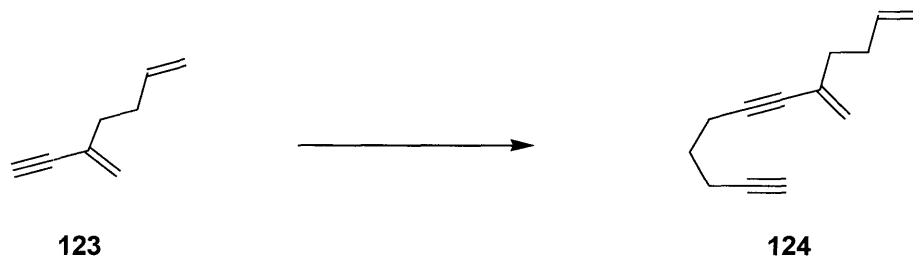
4-Acetyl-6-(cyclopropyl)indan (**120**).

A threaded Pyrex tube (ca. 60 mL capacity) equipped with a rubber septum and argon inlet needle was charged with 10-cyclopropyl-10-undecen-3,8-diyn-2-one (**118**) (0.372 g, 1.86 mmol), phenol (0.177 g, 1.88 mmol), and 18.6 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles, and the tube was then sealed under argon with a threaded Teflon cap. The reaction mixture was heated in an oil bath at 180 °C for 7 h and then allowed to cool to rt. Concentration afforded 0.571 g of a brown oil which was purified by column chromatography on 60 g of silica gel (elution with 2% EtOAc-hexanes) to give 0.186 g (50%) of **120** as a yellow oil: IR (film) 3065, 1670, 1455, and 1350 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.42 (s, 1H), 7.10 (s, 1H), 3.20 (t, $J = 7.5$ Hz, 2H), 2.87 (t, $J = 7.5$ Hz, 2H), 2.07 (quintet, $J = 7.5$ Hz, 2H), 1.94 (m, 1H), 0.99 (m, 2H), and 0.71 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 199.9, 146.5, 142.5, 142.2, 133.8, 125.7, 125.5, 34.0, 32.6, 28.8, 25.6, 15.5, and 9.4; HRMS m/z calcd for $\text{C}_{14}\text{H}_{16}\text{O}$: 200.1201; found: 200.1199.

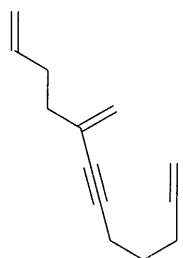




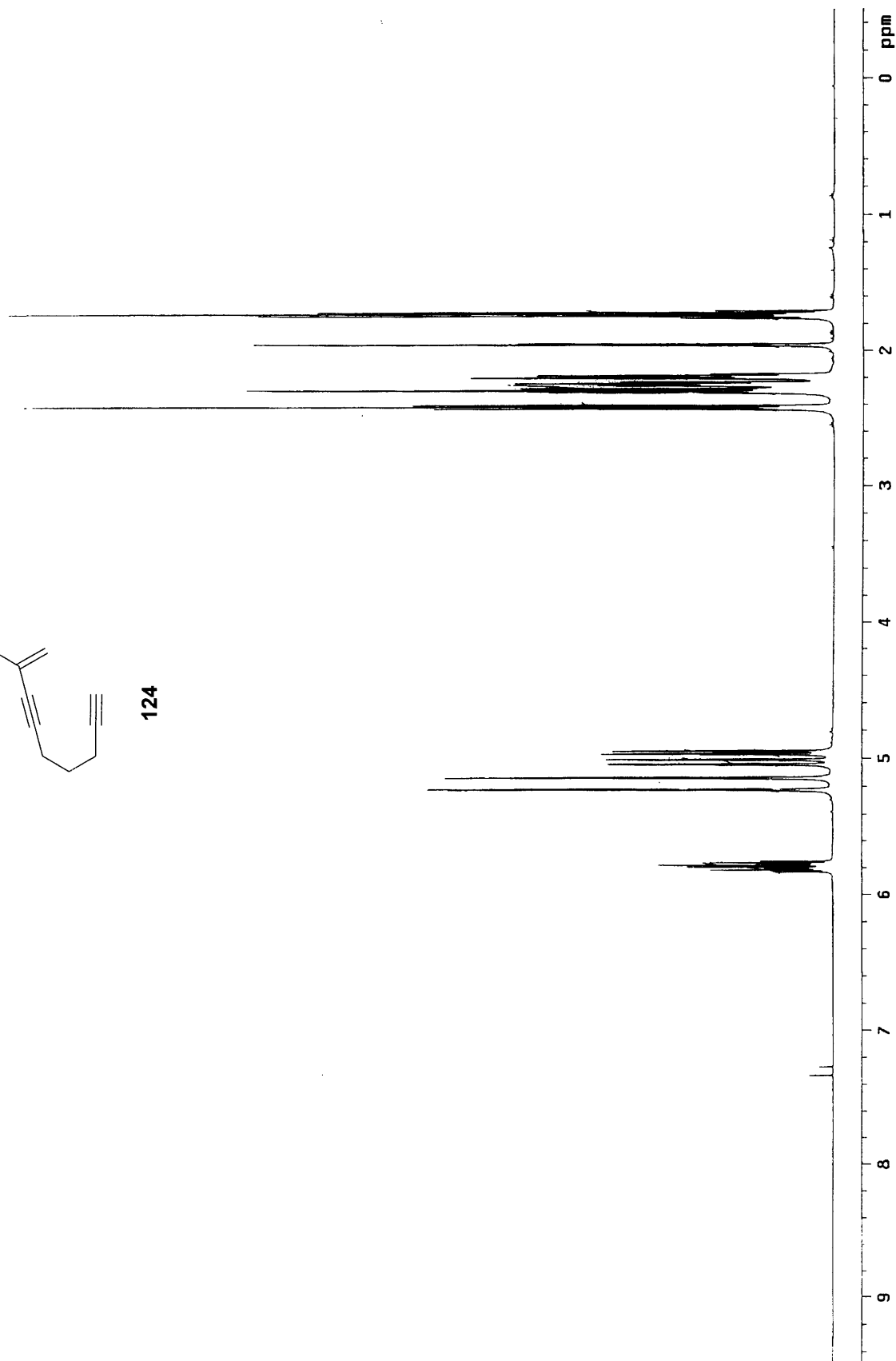
3-Methylene-6-hepten-1-yne (123). A 1-L, three-necked, round-bottomed flask equipped with a rubber septum, mechanical stirrer, and an argon inlet adaptor was charged with 2-methyl-1-buten-3-yne (**122**) (3.0 mL, 2.1 g, 31 mmol) and 220 mL THF and cooled at $-78\text{ }^{\circ}\text{C}$ while 27 mL of *n*-BuLi solution (2.49 M in hexane, 67 mmol) was added dropwise over 10 min. Potassium *t*-butoxide solution (65 mL, 1.03 M in THF, 67 mmol) was added over 2 min and the resulting mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min and then at $-20\text{ }^{\circ}\text{C}$ while a solution of LiBr (6.2 g, 71 mmol) in 25 mL of THF was added via cannula over 3 min. The reaction mixture was cooled to $-78\text{ }^{\circ}\text{C}$ and allyl bromide (2.7 mL, 3.8 g, 31 mmol) was added dropwise via syringe over 2 min. The resulting mixture was allowed to slowly warm to rt. After 11 h, the reaction was cooled to $-40\text{ }^{\circ}\text{C}$ and treated with 100 mL of water. The resulting mixture was allowed to warm to rt, the aqueous layer was separated and extracted with three 200-mL portions of diethyl ether, and the combined organic phases were washed with 1 L of satd NaCl solution, dried over MgSO_4 , filtered, and concentrated (ca. 20 mmHg) to furnish 14.3 g of yellow oil. Column chromatography on 200 g of silica gel (elution with pentane) provided 1.54 g (47%) of **123** (containing ca. 8% pentane) as a colorless oil used in the next step without further purification: IR (film) 3290, 3070, 2970, 2100, 1600, and 1440 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.82 (ddt, $J = 17.4, 10.1, 6.3\text{ Hz}$, 1H), 5.45 (s, 1H), 5.32 (s, 1H), 5.07 (d, $J = 17.4\text{ Hz}$, 1H), 5.00 (d, $J = 10.0\text{ Hz}$, 1H), 2.91 (s, 1H), and 2.24–2.34 (m, 4H).

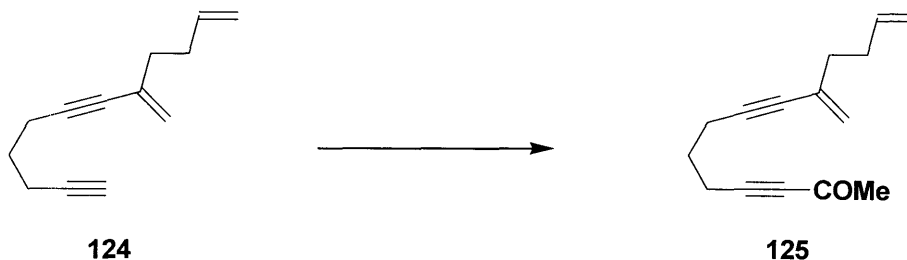


5-Methylene-1-dodecen-6,11-diyn-3-ol (124). A 100-mL, three-necked, round-bottomed flask equipped with two rubber septa and an argon inlet adapter was charged with 0.45 g of 3-methylene-6-hepten-1-yne solution (**123**) (92% wt in pentane, 3.9 mmol) and 7 mL of THF, and cooled at $-50\text{ }^{\circ}\text{C}$ while 1.4 mL of *n*-BuLi solution (2.49 M in hexanes, 3.5 mmol) was added rapidly by syringe. After 2 h, a solution of 5-iodo-1-pentyne (0.60 g, 3.1 mmol) in 6.1 mL of HMPA was added via cannula over 2 min. The resulting mixture was allowed to warm to rt and stirred for 17 h and then treated with 5 mL of satd NH_4Cl solution, 50 mL of pentane and 50 mL of water, and the aqueous phase was separated and extracted with three 30-mL portions of pentane and the combined organic phases were washed with 100 mL of satd NaCl solution, dried over MgSO_4 , filtered, and concentrated (ca. 20 mmHg) to give 0.659 g of a brown oil. Column chromatography on 66 g of silica gel (elution with pentane) yielded 0.437 g (82%) of **124** as a colorless oil: IR (film) 32901, 3060, 2920, 2210, 2110, 1630, and 1430 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.79 (ddt, $J = 17.3, 10.0, 6.3\text{ Hz}$, 1H), 5.22 (d, $J = 1.5\text{ Hz}$, 1H), 5.14 (d, $J = 1.5\text{ Hz}$, 1H), 5.03 (dd, $J = 17.3, 1.8\text{ Hz}$, 1H), 4.96 (dd, $J = 10.0, 1.8\text{ Hz}$, 1H), 2.42 (t, $J = 7.0\text{ Hz}$, 2H), 2.30 (dt, $J = 7.0, 2.6\text{ Hz}$, 2H), 2.23–2.29 (m, 2H), 2.17–2.23 (m, 2H), and 1.74 (quintet, $J = 7.0\text{ Hz}$, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 138.4, 131.9, 120.8, 115.6, 89.6, 84.1, 82.1, 69.6, 37.6, 33.0, 28.3, 19.0, and 18.2; GC-MS m/z : 172 (M^+).

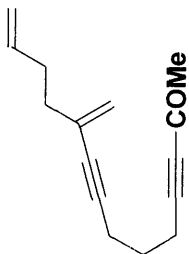


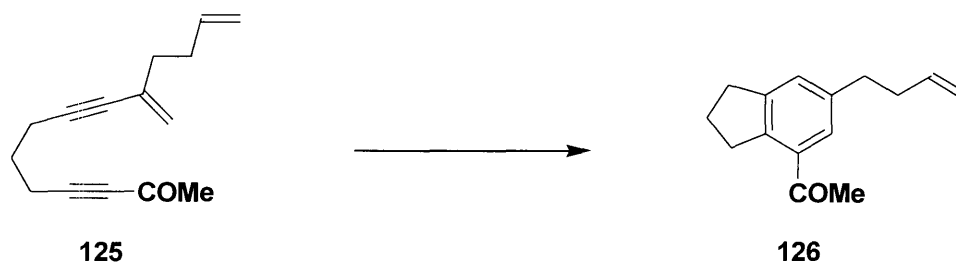
124





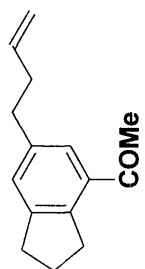
10-Methylene-13-tetradecen-3,8-diyn-2-one (125). A 100-mL, three-necked, round-bottomed flask equipped with two rubber septa and an argon inlet adapter was charged with 5-methylene-1-dodecene-6,11-diyne (**124**) (0.268 g, 1.56 mmol) and 13 mL of THF and then cooled at $-50\text{ }^{\circ}\text{C}$ while 0.68 mL of *n*-BuLi solution (2.49 M in hexane, 1.7 mmol) was added dropwise over 3 min. A 100-mL, three-necked, round-bottomed flask equipped with two rubber septa and an argon inlet adapter was charged with acetic anhydride (0.22 g, 0.21 mL, 2.2 mmol) and 2.6 mL of THF and then cooled at $-50\text{ }^{\circ}\text{C}$ while the solution of lithium acetylide was added via cannula over 4 min (1-mL THF rinse). The resulting mixture was allowed to warm to rt over 18.5 h and then was cooled at $-50\text{ }^{\circ}\text{C}$ while 8 mL of satd NH_4Cl and 0.5 mL of satd NH_4OH solutions were added. The resulting mixture was diluted with 50 mL of water and 50 mL of diethyl ether, and the aqueous phase was separated and extracted with three 50-mL portions of diethyl ether. The combined organic phases were washed with 100 mL of satd NaCl solution, dried over MgSO_4 , filtered, and concentrated to furnish 0.433 g of yellow oil. Column chromatography on 43 g of silica gel (elution with 3% EtOAc-hexanes) yielded 0.025 g of unreacted alkyne **124** and 0.274 g (82%, 91% based on recovered starting material) of **125** as a yellow oil: IR (film) 3075, 2935, 2210, 1745, and 1425 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.80 (ddt, $J = 17.2, 10.1, 6.3\text{ Hz}$, 1H), 5.24 (d, $J = 1.5\text{ Hz}$, 1H), 5.16 (d, $J = 1.5\text{ Hz}$, 1H), 5.03 (dd, $J = 17.2, 1.6\text{ Hz}$, 1H), 4.97 (dd, $J = 10.1, 1.6\text{ Hz}$, 1H), 2.50 (t, $J = 7.0\text{ Hz}$, 2H), 2.44 (t, $J = 7.0\text{ Hz}$, 2H), 2.32 (s, 3H), 2.23–2.29 (m, 2H), 2.17–2.23 (m, 2H), and 1.80 (quintet, $J = 7.0\text{ Hz}$, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 185.5, 138.4, 131.8, 121.2, 115.7, 93.4, 88.9, 82.6, 82.4, 37.5, 33.5, 33.0, 27.5, 19.2, and 18.7; GC-MS m/z : 214 (M^+).



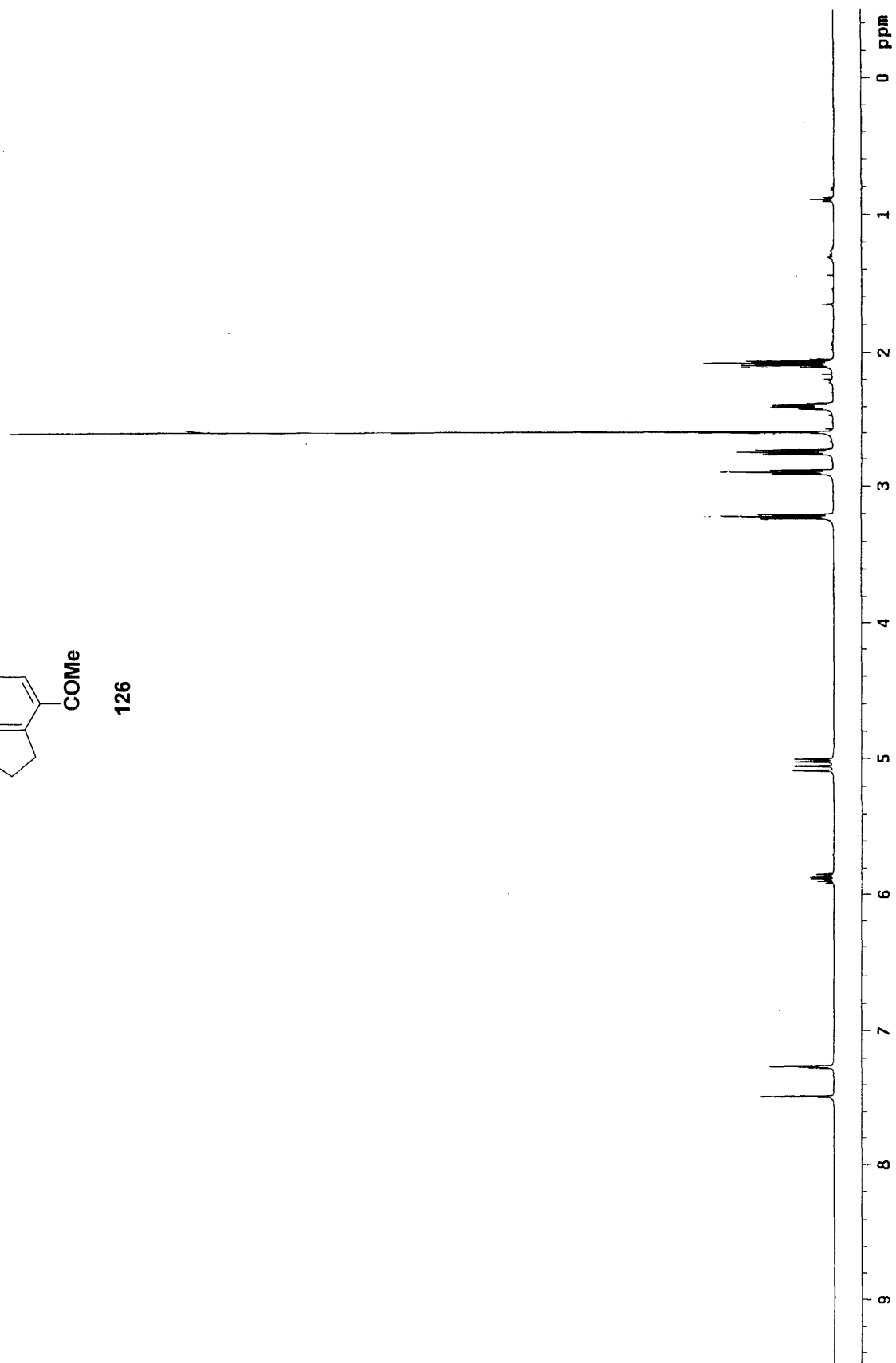


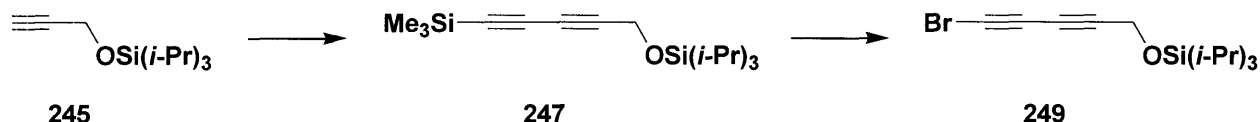
4-Acetyl-6-(3-butenyl)indan (**126**).

A threaded Pyrex tube (ca. 20 mL capacity) equipped with a rubber septum and argon inlet needle was charged with 10-methylene-13-tetradecen-3,8-diyn-2-one (**125**) (0.089 g, 0.41 mmol), phenol (0.039 g, 0.41 mmol), and 4.1 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles, and the tube was then sealed under argon with a threaded Teflon cap. The reaction mixture was heated in an oil bath at 180 °C for 7 h and then allowed to cool to rt. Concentration afforded 0.152 g of a brown oil which was purified by column chromatography on 15 g of silica gel (elution with 3% EtOAc-hexanes) to give 0.043 g (48%) of **126** as a yellow oil: IR (film) 3075, 1675, 1430, and 1365 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.49 (s, 1 H), 7.26 (s, 1 H), 5.87 (ddt, $J = 17.1, 10.4, 6.6$ Hz, 1 H), 5.07 (dd, $J = 17.1, 1.8$ Hz, 1 H), 5.01 (dd, $J = 10.4, 1.8$ Hz, 1 H), 3.22 (t, $J = 7.5$ Hz, 2 H), 2.90 (t, $J = 7.5$ Hz, 2 H), 2.75 (t, $J = 7.8$ Hz, 2 H), 2.59 (s, 3 H), 2.40 (m, 2 H), and 2.09 (quintet, $J = 7.5$ Hz, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ 200.2, 146.7, 143.1, 140.2, 138.0, 134.0, 129.0, 127.8, 115.4, 35.9, 35.2, 34.0, 32.5, 28.7, and 25.4; HRMS m/z calcd for $\text{C}_{15}\text{H}_{18}\text{O}$: 214.1358; found: 214.1361.



126



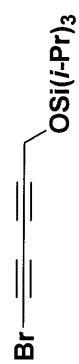


1-Bromo-5-(triisopropylsiloxy)-1,3-pentadiyne (**249**).

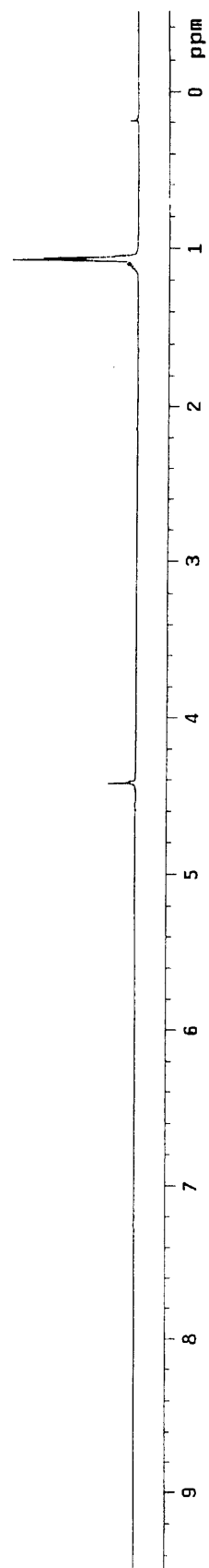
A 200-mL, three-necked, round-bottomed flask equipped with two rubber septa, an argon inlet needle, and a short path distillation head fitted with a 100-mL, collection flask was charged with alkyne **245** (3.177 g, 14.96 mmol) and 24 mL of THF. The solution was cooled at $-78\text{ }^{\circ}\text{C}$ while 6.24 mL of *n*-BuLi solution (2.40 M in hexanes, 15.0 mmol) was added via syringe over 10 min, and the pale yellow solution was allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 20 min. The dry ice-acetone bath was replaced with an ice bath and the solution was stirred at $0\text{ }^{\circ}\text{C}$ while CuI (2.848 g, 14.95 mmol) was added in one portion. The ice bath was removed and the yellow, viscous mixture was stirred at rt for 30 min. Next, THF and hexane were removed by distillation (rt, 0.5 mmHg) while cooling the collection flask at $-78\text{ }^{\circ}\text{C}$. The remaining copper acetylide was dried at 0.5 mmHg for 30 min, and then the system was vented to argon and 48 mL of pyridine was added. 1-Iodo-2-(trimethylsilyl)acetylene (**238**) (2.95 g, 15.0 mmol) was added via cannula in one portion (2-mL pyridine rinse), and the resulting viscous suspension was stirred at rt for 1 h. The reaction mixture was diluted with 300 mL of hexane and washed with three 200-mL portions of conc NH_4OH solution. The combined aqueous layers were diluted with 250 mL of satd NaCl solution, extracted with four 200-mL portions of hexane, and the combined organic layers were dried over MgSO_4 , filtered, and concentrated to afford 3.735 g of a dark brown oil. Two successive purifications by column chromatography on 120 g of silica gel (gradient elution with 0–0.5% EtOAc-hexanes) provided 1.623 g (35%) of diyne **247** as a deep yellow oil.

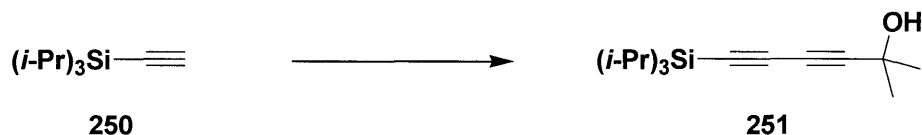
A 100-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with diyne **247** (1.616 g, 5.236 mmol), NBS (1.027 g, 5.770 mmol), and 35 mL of acetone. Silver(I) nitrate (0.136 g, 0.801 mmol) was added in one portion, the flask was wrapped with aluminum foil, and the resulting suspension was stirred at rt for 15 h. The reaction mixture was diluted with 100 mL of pentane, washed with three 100-mL portions of satd $\text{Na}_2\text{S}_2\text{O}_3$ solution and 100 mL of satd NaCl solution, dried over MgSO_4 , filtered, and concentrated to give 1.224 g (74%) of bromo diyne **249** as an orange oil contaminated with 4% of unreacted **247**. This material was dissolved in 6.1 mL of benzene and stored at $-20\text{ }^{\circ}\text{C}$ as a 0.60 M stock solution. Data for **249**: IR (neat) 2944, 2867, 2239, 2108, and 1462 cm^{-1} ; ^1H NMR (500 MHz,

CDCl₃) δ 4.43 (s, 2H), 1.10 (sept, J = 6.3 Hz, 3H), and 1.09 (d, J = 6.3 Hz, 18H); ¹³C NMR (125 MHz, CDCl₃) δ 74.1, 69.8, 67.9, 65.2, 52.4, 18.1, and 12.2; HRMS-ESI m/z : [M+Na]⁺ calcd for C₁₄H₂₃BrOSi, 337.0594; found, 337.0607.



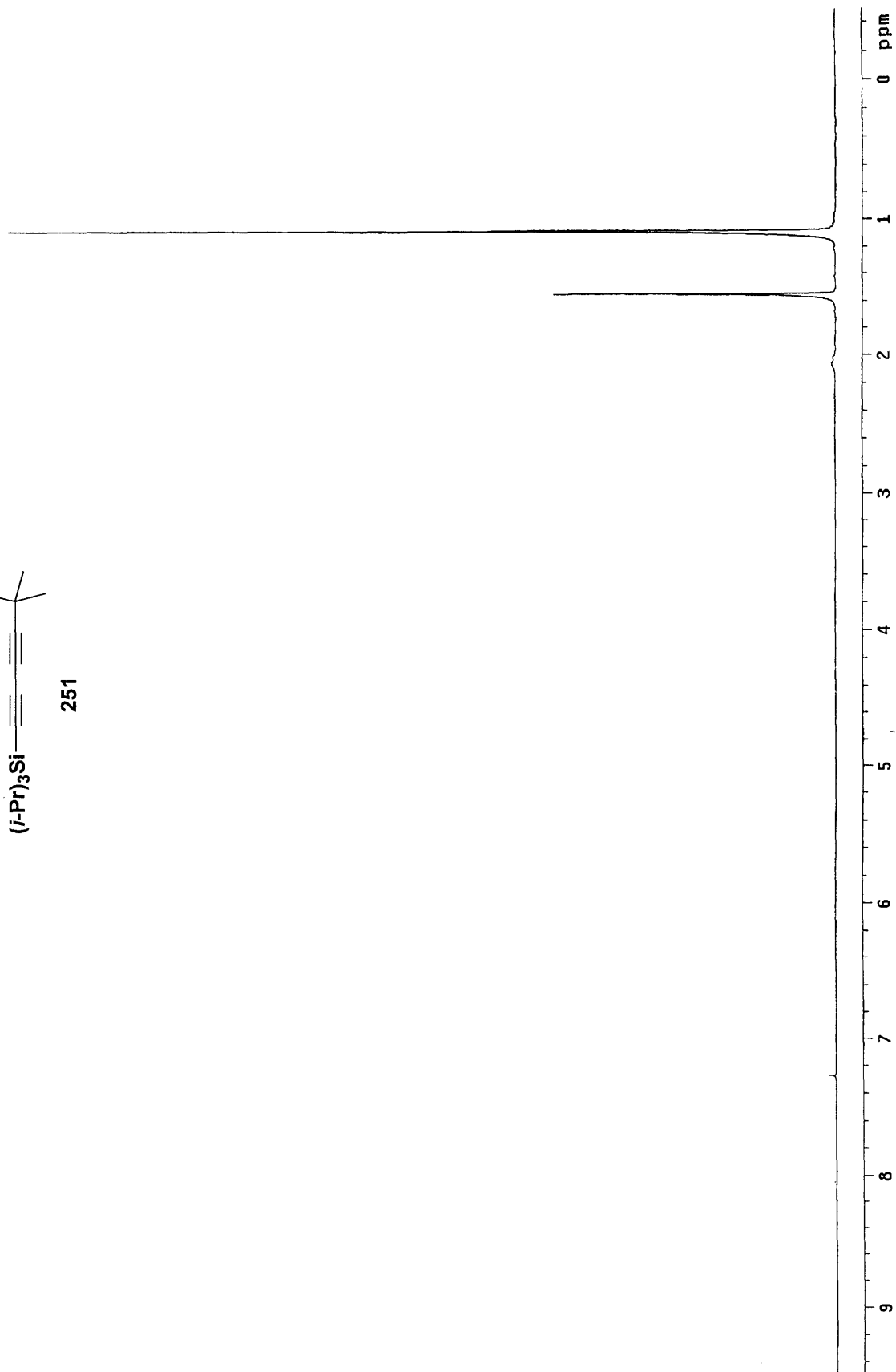
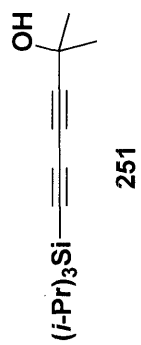
249

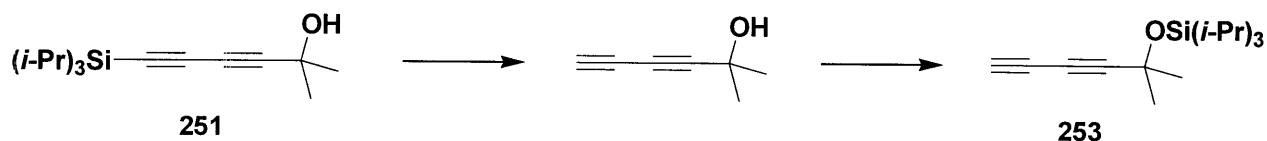




5-Hydroxy-1-(triisopropylsilyl)-5-methyl-1,3-hexadiyne (251).

A 100-mL, three-necked, round-bottomed flask equipped with two glass stoppers and an argon inlet adapter was charged with CuCl (0.097 g, 0.98 mmol) and 40 mL of aqueous butylamine (30% wt in H₂O) solution. A few crystals of NH₂OH•HCl were added until the blue solution became colorless (ca. 0.010 g). Triisopropylsilyl acetylene (**250**) (13 mL, 11 g, 58 mmol) was added in one portion, and the mixture was cooled at 0 °C while 1-bromo-3-hydroxy-3-methylbutyne (**234**) (7.8 g, 48 mmol) was added via cannula over 5 min. The ice bath was removed and the reaction mixture was allowed to stir at rt for 30 min while crystals of NH₂OH•HCl were added (ca. 0.010 g portions) as necessary to prevent the mixture from turning blue or green. The resulting beige mixture was extracted with six 50-mL portions of Et₂O, and the combined organic layers were dried over MgSO₄, filtered, and concentrated to give 13.653 g of a white solid. Column chromatography on 150 g of silica gel (gradient elution with 0–50% EtOAc-hexanes) provided 5.743 g (45%) of diyne **251** as a white solid: mp 53–55 °C; IR (film) 3339, 2944, 2866, 2230, 2101, and 1462 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 2.06 (br s, 1H), 1.55 (s, 6H), and 1.09 (s, 21H); ¹³C NMR (125 MHz, CDCl₃) δ 89.0, 85.1, 80.8, 67.9, 65.8, 31.3, 18.7, and 11.4; GC-MS *m/z*: 264 (M⁺).

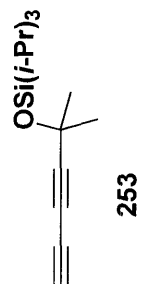


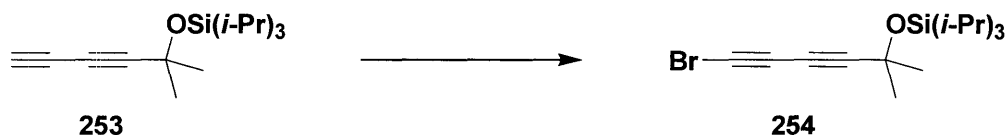


2-(Triisopropyl)-2-methyl-3,5-hexadiyne (**253**).

A 250-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with diyne **251** (5.703 g, 21.56 mmol) and 150 mL of THF. The solution was cooled at 0 °C while 28 mL of *n*-Bu₄NF solution (1.0 M in THF, 28 mmol) was added via syringe, and the resulting yellow solution was stirred at 0 °C for 10 min. The reaction mixture was diluted with 150 mL of Et₂O, 150 mL of water, and 50 mL of satd NaCl solution. The aqueous layer was separated and extracted with two 150-mL portions of Et₂O, and the combined organic layers were washed with 300 mL of satd NaCl solution, dried over MgSO₄, filtered, and concentrated to provide 5.556 g of a dark red oil. Column chromatography on 80 g silica gel (gradient elution with 3–5% EtOAc-hexanes) provided 1.952 g (84%, 90% pure by ¹H NMR analysis) of the desired desilylated diyne as an orange oil contaminated with triisopropylsilanol.

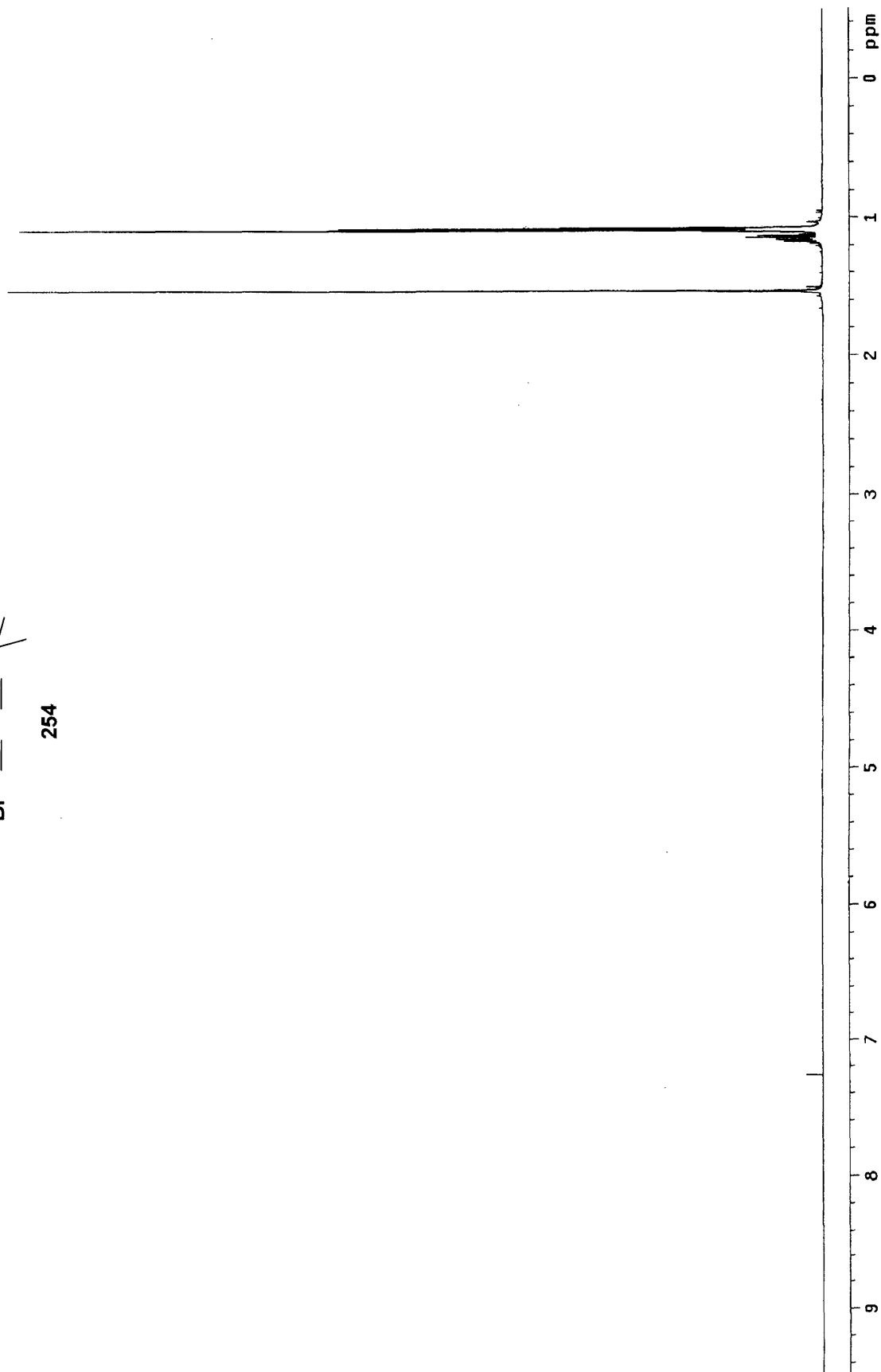
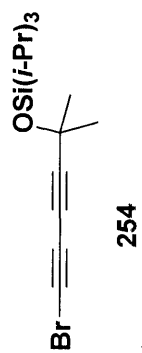
A 250-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with desilylated diyne (1.906 g, 90% purity, ca. 15 mmol) and 100 mL of CH₂Cl₂. The solution was cooled at 0 °C while 2,6-lutidine (2.6 mL, 2.4 g, 22 mmol) and triisopropylsilyl triflate (4.8 mL, 5.5 g, 18 mmol) were added sequentially via syringe. The ice bath was then removed and the reaction mixture was heated at reflux for 36 h and then allowed to cool to room temperature. The solution was washed with two 50-mL portions of 5% HCl, 50 mL of water, 50 mL of satd NaCl solution, dried over MgSO₄, filtered, and concentrated to provide 4.386 g of an orange oil. Column chromatography on 100 g silica gel (elution with pentanes) provided 3.250 g (57% overall from **251**) of diyne **253** as a colorless oil: IR (neat) 3314, 2944, 2867, 2230, 2063, and 1464 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 2.18 (s, 1H), 1.54 (s, 6H), 1.15 (sept, *J* = 6.4 Hz, 3H), and 1.09 (d, *J* = 6.4 Hz, 18H); ¹³C NMR (125 MHz, CDCl₃) δ 81.8, 68.4, 67.9, 67.2, 66.6, 33.0, 18.5, and 13.1; GC-MS *m/z*: 264 (M⁺).

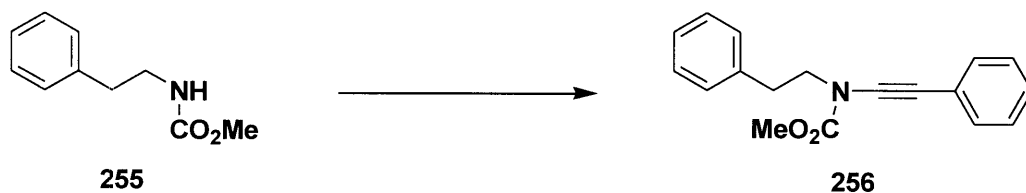




1-Bromo-5-(triisopropylsiloxy)-5-methyl-1,3-hexadiyne (254).

A 100-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with diyne **253** (3.201 g, 12.10 mmol), NBS (3.225 g, 18.12 mmol), and 40 mL of acetone. Silver(I) nitrate (0.215 g, 1.27 mmol) was added in one portion, the flask was wrapped with aluminum foil, and the resulting suspension was stirred at rt for 20 h. The reaction mixture was then diluted with 200 mL of hexanes, washed with five 50-mL portions of satd $\text{Na}_2\text{S}_2\text{O}_3$ solution, and the combined aqueous layers were back-extracted with three 50-mL portions of hexane. The combined organic layers were washed with 200 mL of satd NaCl solution, dried over MgSO_4 , filtered, and concentrated to afford 4.075 g (98%) of bromo diyne **254** as an orange oil which was dissolved in 20 mL of benzene and stored at $-20\text{ }^\circ\text{C}$ as a 0.58 M stock solution. Data for **254**: IR (neat) 2962, 2867, 2248, 2136, and 1464 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.53 (s, 6H), 1.14 (sept, $J = 6.4\text{ Hz}$, 3H), and 1.08 (d, $J = 6.4\text{ Hz}$, 18H); ^{13}C NMR (125 MHz, CDCl_3) δ 80.5, 67.9, 66.6, 65.1, 41.3, 33.1, 18.5, and 13.1. HRMS-ESI m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{27}\text{BrOSi}$, 365.0907; found, 365.0894.

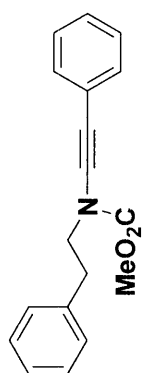




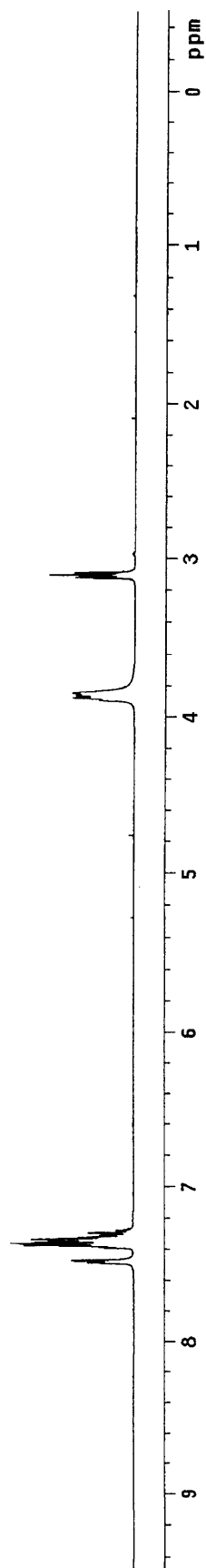
General Procedure for the Coupling of Amide Derivatives with Bromo Alkynes.

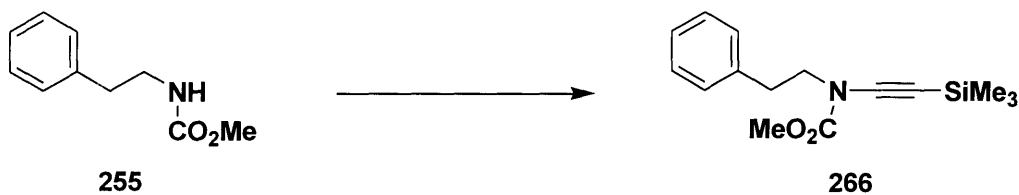
N-Methoxycarbonyl-*N*-(2-phenylethyl)-2-phenylethynylamine (**256**).

A 250-mL, two-necked, round-bottomed flask equipped with a rubber septum and addition funnel fitted with a rubber septum and argon inlet needle was charged with carbamate **255** (1.951 g, 10.89 mmol) and 44 mL of pyridine. The solution was cooled at 0 °C while 12 mL of KHMDS solution (0.91 M in THF, 11 mmol) was added via syringe over 4 min. The reaction mixture was stirred at 0 °C for 10 min and then a solution of CuI (2.073 g, 10.89 mmol) in 22 mL of pyridine was added via cannula in one portion (10-mL pyridine rinse). The ice bath was removed, and the resulting solution was stirred at room temperature for 2 h. A solution of 1-bromo-2-phenylacetylene (**224**) (36 mL, 0.60 M in benzene, 22 mmol) was then added via the addition funnel over 1 h, and the resulting mixture was stirred at room temperature for 20 h. The reaction mixture was diluted with 300 mL of Et₂O and washed with three 100-mL portions of a 2:1 mixture of satd NaCl and concentrated NH₄OH. The combined aqueous layers were extracted with three 75-mL portions of Et₂O, and the combined organic layers were washed with 300 mL of satd NaCl, dried over MgSO₄, filtered, and concentrated to provide 4.397 g of a dark red oil. Column chromatography on 120 g of silica gel (gradient elution with 0–3% EtOAc-hexanes) provided 2.309 g (76%) of ynamide **256** as a yellow oil: IR (neat): 3028, 2953, 2245, 1729, 1600, 1496, 1442, 1395, 1363, 1307, 1245, and 1147 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.48 (d, *J* = 6.7 Hz, 2H), 7.28–7.39 (m, 8H), 3.88 (t, *J* = 7.5 Hz, 2H), 3.84 (s, 3H), and 3.11 (t, *J* = 7.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 155.6, 138.0, 131.4, 129.0, 128.6, 128.3, 127.7, 126.7, 123.2, 82.7, 71.0, 54.1, 51.4, and 34.2; HRMS-ESI *m/z*: [M+Na]⁺ calcd for C₁₈H₁₇NO₂, 302.1151; found, 302.1141. Anal. Calcd for C₁₈H₁₇NO₂: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.26; H, 6.23; N, 5.32.



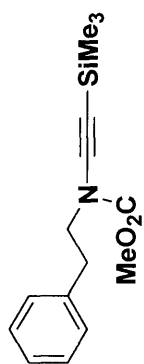
256



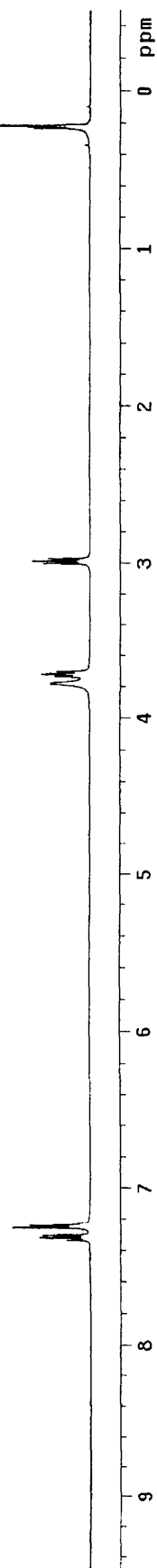


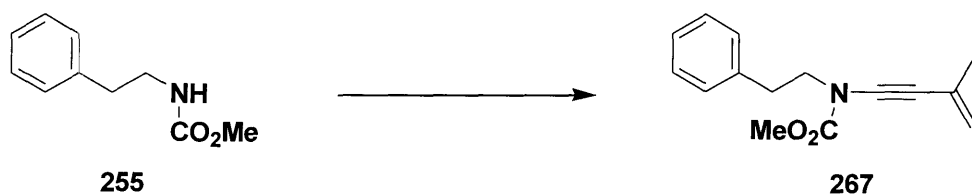
***N*-Methoxycarbonyl-*N*-(2-phenylethyl)-2-(trimethylsilyl)ethynylamine (**266**).**

Reaction of a solution of carbamate **255** (0.157 g, 0.876 mmol) in 3.5 mL of pyridine with KHMDS (0.97 mL, 0.91 M in THF, 0.88 mmol), CuI (0.167 g, 0.877 mmol) in 2.3 mL of pyridine, and 1-bromo-2-(trimethylsilyl)acetylene (**241**) (2.9 mL, 0.60 M in benzene, 1.7 mmol) according to the general procedure gave 0.282 g of a dark red oil. Column chromatography on 25 g of silica gel (gradient elution with 0–5% EtOAc-hexanes) provided 0.135 g (56%) of ynamide **266** as a pale yellow oil: IR (neat): 3029, 2956, 2898, 2176, 1736, 1604, 1498, 1443, 1375, 1282, 1249, 1202, and 1124 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.32 (m, 2H), 7.25 (m, 3H), 3.78 (s, 3H), 3.72 (t, $J = 7.6$ Hz, 2H), 2.99 (t, $J = 7.6$ Hz, 2H), and 0.22 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 155.5, 138.0, 128.9, 128.6, 126.6, 95.4, 72.9, 54.0, 51.2, 33.9, and 0.3; HRMS-EI m/z : $[\text{M}]^+$ calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_2\text{Si}$, 275.1337; found, 275.1341.



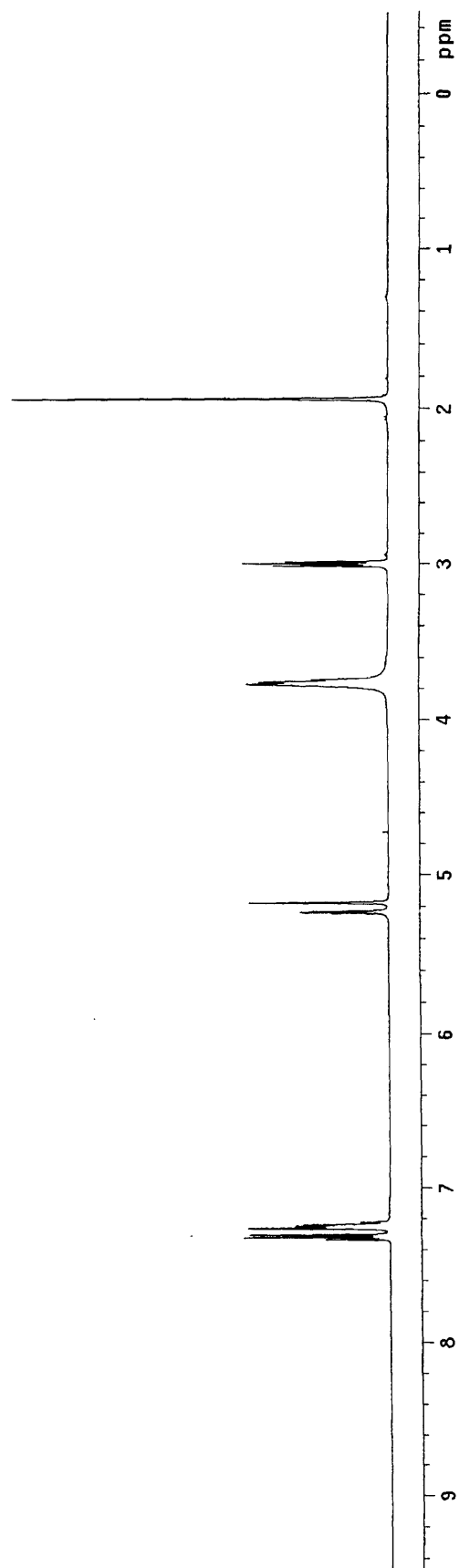
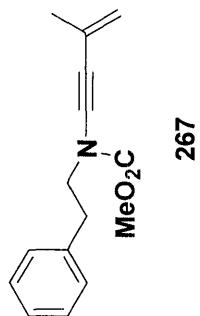
266

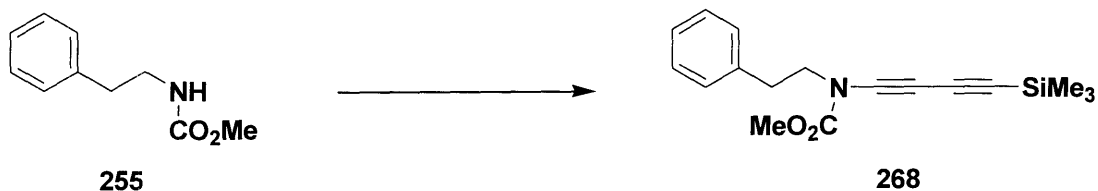




***N*-Methoxycarbonyl-*N*-(2-phenylethyl)-3-methyl-3-buten-1-ynylamine (**267**).**

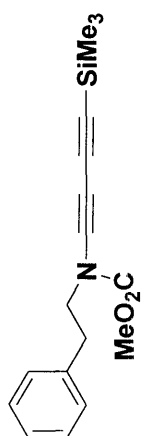
Reaction of a solution of carbamate **255** (0.244 g, 1.36 mmol) in 5.4 mL of pyridine with KHMDS (1.5 mL, 0.91 M in THF, 1.4 mmol), CuI (0.260 g, 1.37 mmol) in 3.7 mL of pyridine, and 1-bromo-3-methyl-3-buten-1-yne (**231**) (4.7 mL, 0.58 M in benzene, 2.7 mmol) according to the general procedure gave 0.486 g of a dark red oil. Column chromatography on 35 g of silica gel (gradient elution with 0–3% EtOAc-hexanes) afforded 0.216 g (65%) of ynamide **267** as a pale yellow oil: IR (neat): 3028, 2954, 2234, 1730, 1614, 1497, 1444, 1402, 1367, 1309, 1280, 1251, and 1177 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.32 (m, 2H), 7.25 (m, 3H), 5.23 (s, 1H), 5.17 (s, 1H), 3.77 (s, 3H), 3.76 (t, $J = 7.5$ Hz, 2H), 3.00 (t, $J = 7.5$ Hz, 2H), and 1.94 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 155.4, 137.9, 128.9, 128.5, 126.6, 126.3, 119.5, 82.0, 72.3, 53.9, 51.2, 34.1, and 23.7; HRMS-ESI m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{15}\text{H}_{17}\text{NO}_2$, 266.1151; found, 266.1155.



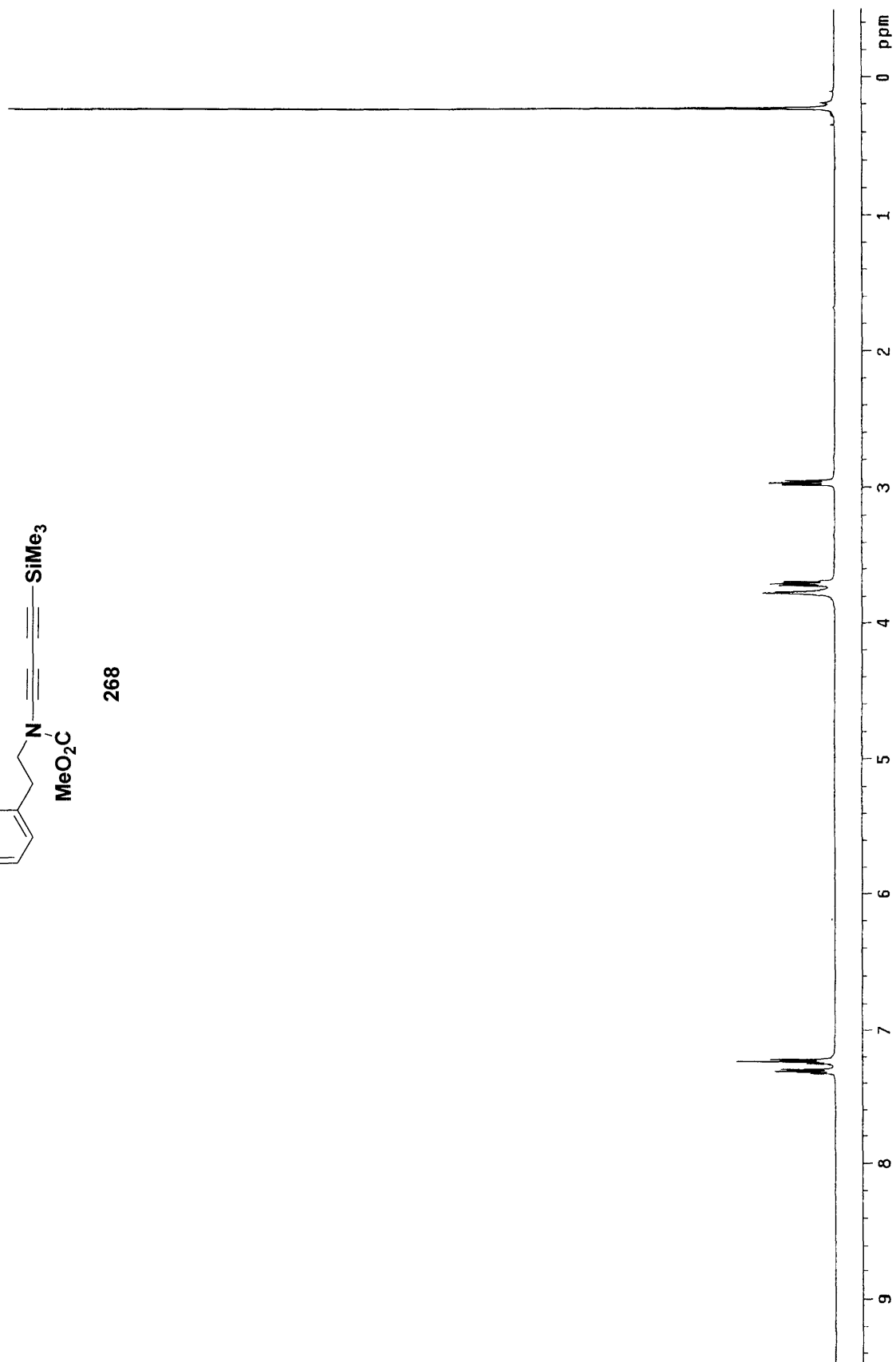


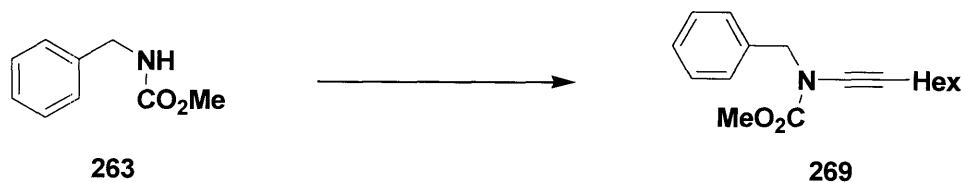
***N*-Methoxycarbonyl-*N*-(2-phenylethyl)-4-(trimethylsilyl)-1,3-butadiynylamine (**268**).**

Reaction of a solution of carbamate **255** (0.195 g, 1.08 mmol) in 4.3 mL of pyridine with KHMDS (1.2 mL, 0.91 M in THF, 1.1 mmol), CuI (0.209 g, 1.10 mmol) in 3.2 mL of pyridine, and 1-bromo-4-(trimethylsilyl)-1,3-butadiyne (**242**) (5.4 mL, 0.40 M in benzene, 2.2 mmol) according to the general procedure gave 0.451 g of a dark red oil. Column chromatography on 40 g of silica gel (gradient elution with 0–2% EtOAc-hexanes) provided 0.128 g (40%) of ynamide **268** as a yellow oil: IR (neat): 3029, 2957, 2232, 2113, 1741, 1604, 1497, 1440, 1396, 1359, 1293, 1250, 1205, and 1131 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.31 (m, 2H), 7.23 (m, 3H), 3.77 (s, 3H), 3.71 (t, $J = 7.8$ Hz, 2H), 2.97 (t, $J = 7.8$ Hz, 2H), and 0.23 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 155.6, 137.5, 129.0, 128.7, 126.9, 90.0, 87.6, 69.5, 58.7, 54.5, 51.2, 34.2, and -0.2 ; HRMS-ESI m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_2\text{Si}$, 300.1414; found, 300.1424.



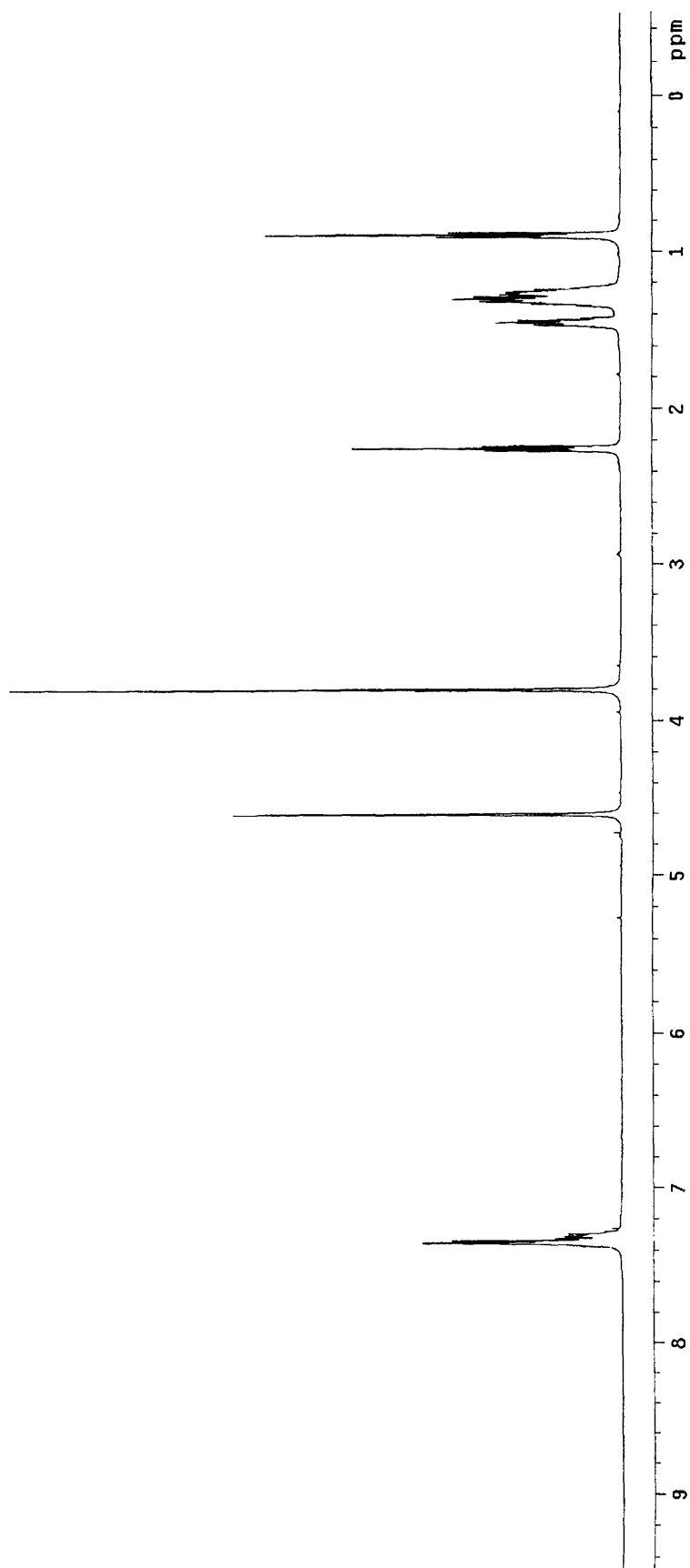
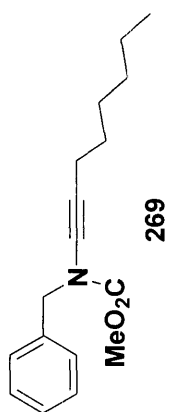
268

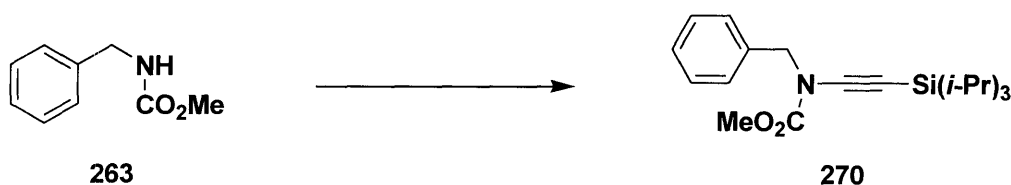




***N*-Benzyl-*N*-methoxycarbonyl-1-octynylamine (269).**

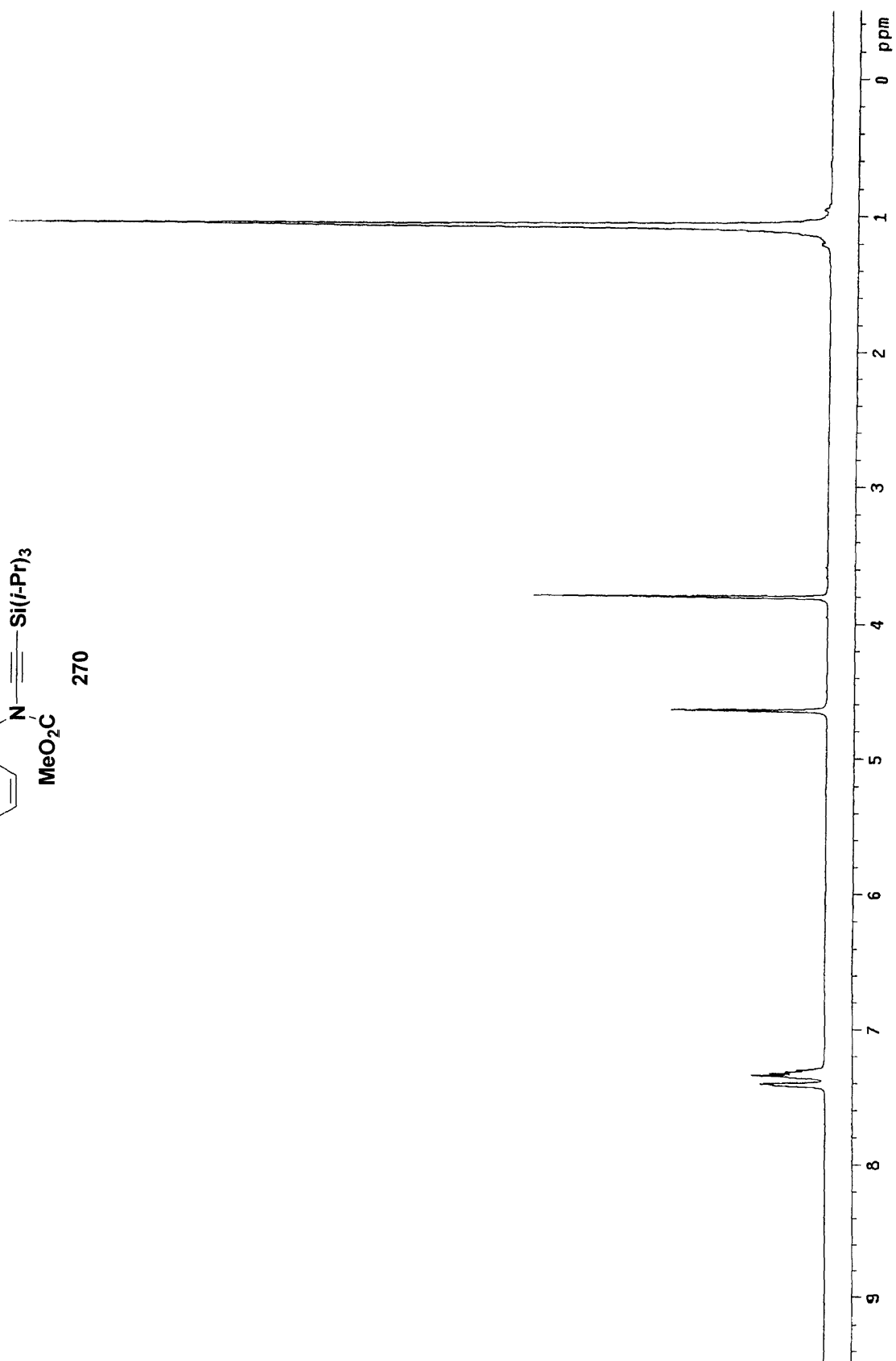
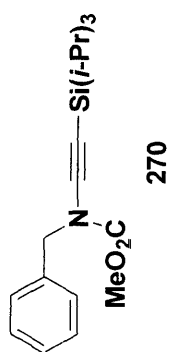
Reaction of a solution of carbamate **263** (0.150 g, 0.908 mmol) in 3.6 mL of pyridine with KHMDS (1.0 mL, 0.91 M in THF, 0.91 mmol), CuI (0.174 g, 0.914 mmol) in 2.8 mL of pyridine, and 1-bromo-1-octyne (**227**) (3.0 mL, 0.60 M in benzene, 1.8 mmol) according to the general procedure gave 0.402 g of a dark brown oil. Column chromatography on 25 g of silica gel (gradient elution with 0–5% EtOAc-hexanes) provided 0.123 g (50%) of ynamide **269** as a red oil: IR (neat): 3033, 2931, 2858, 2263, 1728, 1606, 1497, 1444, 1389, 1360, 1286, 1219, and 1128 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.30–7.37 (m, 5H), 4.60 (s, 2H), 3.80 (s, 3H), 2.25 (t, $J = 7.0$ Hz, 2H), 1.45 (app quintet, $J = 7.0$ Hz, 2H), 1.22–1.35 (m, 6H), and 0.89 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 156.3, 136.4, 128.5, 128.5, 128.0, 73.9, 70.7, 54.0, 54.0, 31.5, 29.0, 28.5, 22.7, 18.5, and 14.2; HRMS-ESI m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_2$, 296.1621; found, 296.1608.

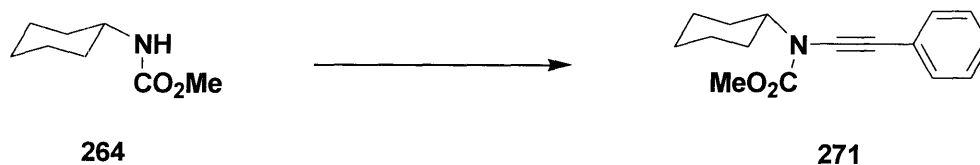




***N*-Benzyl-*N*-methoxycarbonyl-(2-triisopropylsilyl)ethynylamine (**270**).**

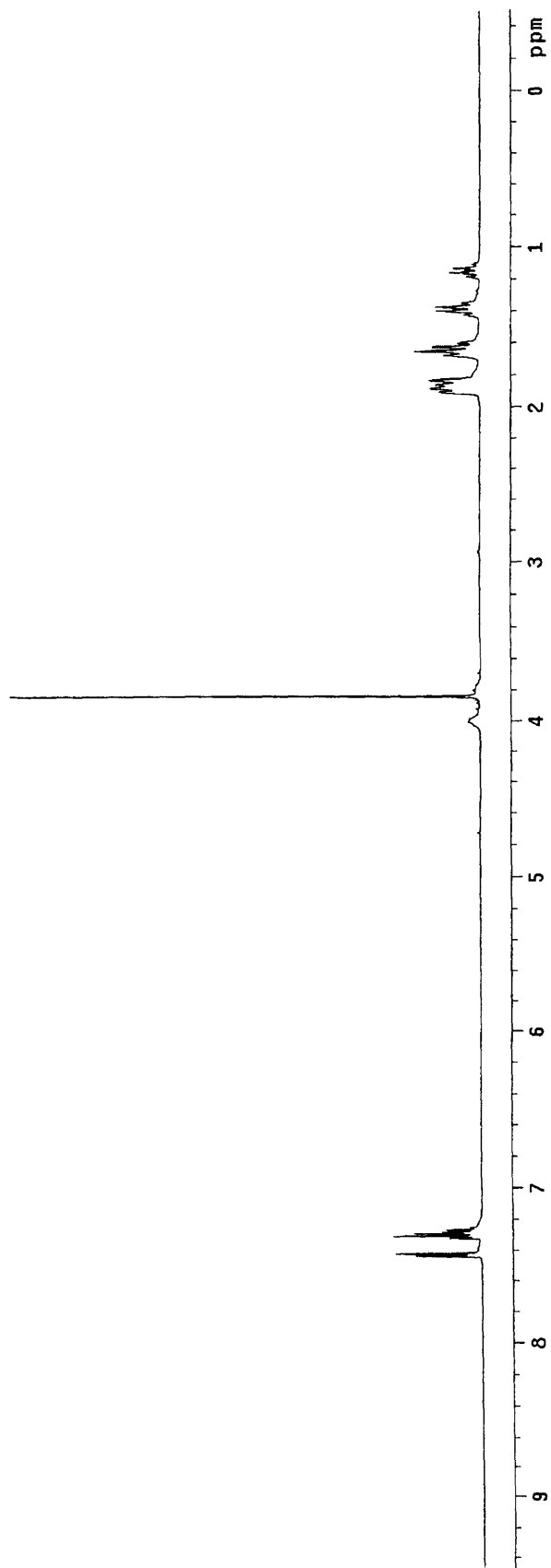
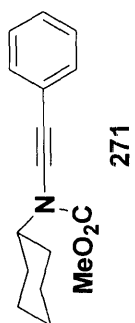
Reaction of a solution of carbamate **263** (0.205 g, 1.24 mmol) in 5.0 mL of pyridine with KHMDS (1.4 mL, 0.91 M in THF, 1.3 mmol), CuI (0.244 g, 1.28 mmol) in 3.5 mL of pyridine, and 1-bromo-2-(triisopropylsilyl)acetylene (**228**) (4.1 mL, 0.60 M in benzene, 2.5 mmol) according to the general procedure gave 0.909 g of a dark red oil. Column chromatography on 35 g of silica gel (gradient elution with 0–5% EtOAc-hexanes) provided 0.317 g (74%) of ynamide **270** as a yellow oil: IR (neat): 3033, 2943, 2865, 2176, 1733, 1606, 1497, 1442, 1370, 1271, 1225, and 1123 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.41 (m, 2H), 7.30–7.36 (m, 3H), 4.64 (s, 2H), 3.80 (s, 3H), and 1.06–1.08 (app s, 21H); ¹³C NMR (125 MHz, CDCl₃) δ 155.8, 135.9, 128.6, 128.5, 128.0, 97.0, 69.2, 53.9, 53.7, 18.6, and 11.4; HRMS-EI *m/z*: [M]⁺ calcd for C₂₀H₃₁NO₂Si, 345.2119; found, 345.2107.

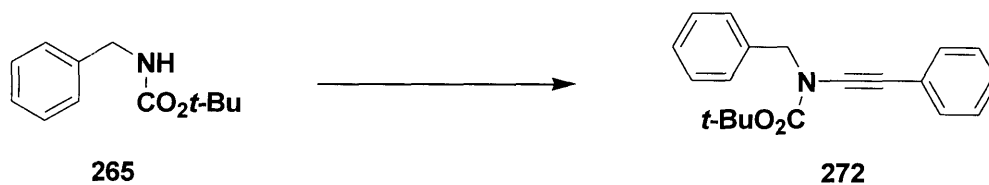




***N*-Cyclohexyl-*N*-methoxycarbonyl-2-phenylethynylamine (**271**).**

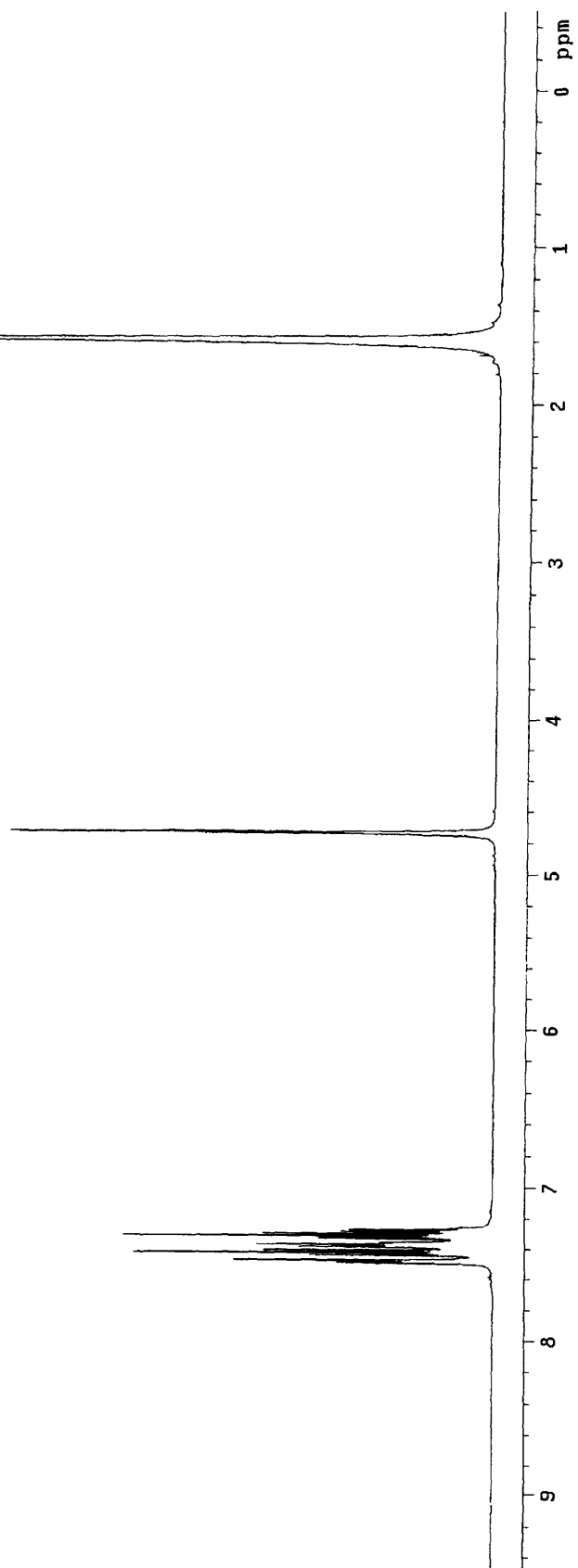
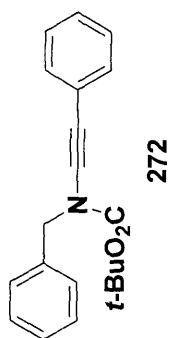
Reaction of a solution of carbamate **264** (0.170 g, 1.08 mmol) in 4.4 mL of pyridine with KHMDS (1.2 mL, 0.91 M in THF, 1.1 mmol), CuI (0.209 g, 1.10 mmol) in 3.2 mL of pyridine, and 1-bromo-2-phenylacetylene (**224**) (3.6 mL, 0.60 M in benzene, 2.2 mmol) according to the general procedure gave 0.501 g of a dark red oil. Column chromatography on 35 g of silica gel (gradient elution with 0–3% EtOAc-hexanes) provided 0.118 g (42%) of ynamide **271** as a yellow oil: IR (neat): 2933, 2857, 2247, 1728, 1599, 1440, 1402, 1357, 1295, and 1245 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.43 (m, 2H), 7.25–7.32 (m, 3H), 3.99 (m, 1H), 3.84 (s, 3H), 1.83–1.91 (m, 4H), 1.60–1.68 (m, 3H), 1.39 (app ddt, *J* = 3.3, 3.3, 13.1 Hz, 2H), and 1.14 (app ddt, *J* = 3.7, 3.7, 13.1 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 155.6, 131.2, 128.4, 127.5, 123.6, 80.7, 72.4, 56.6, 54.0, 30.7, 25.5, and 25.3; HRMS-EI *m/z*: [M]⁺ calcd for C₁₆H₁₉NO₂, 257.1411; found, 257.1414.

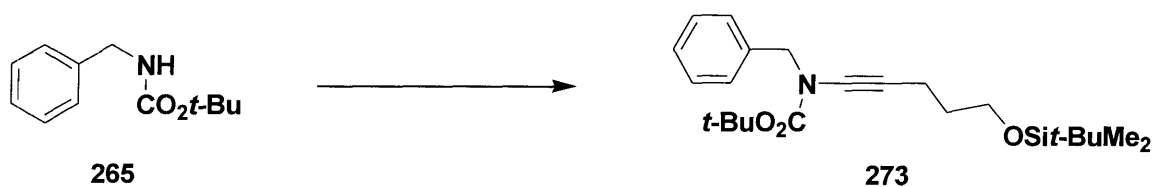




***N*-Benzyl-*N*-tert-butoxycarbonyl-2-phenylethynylamine (272).**

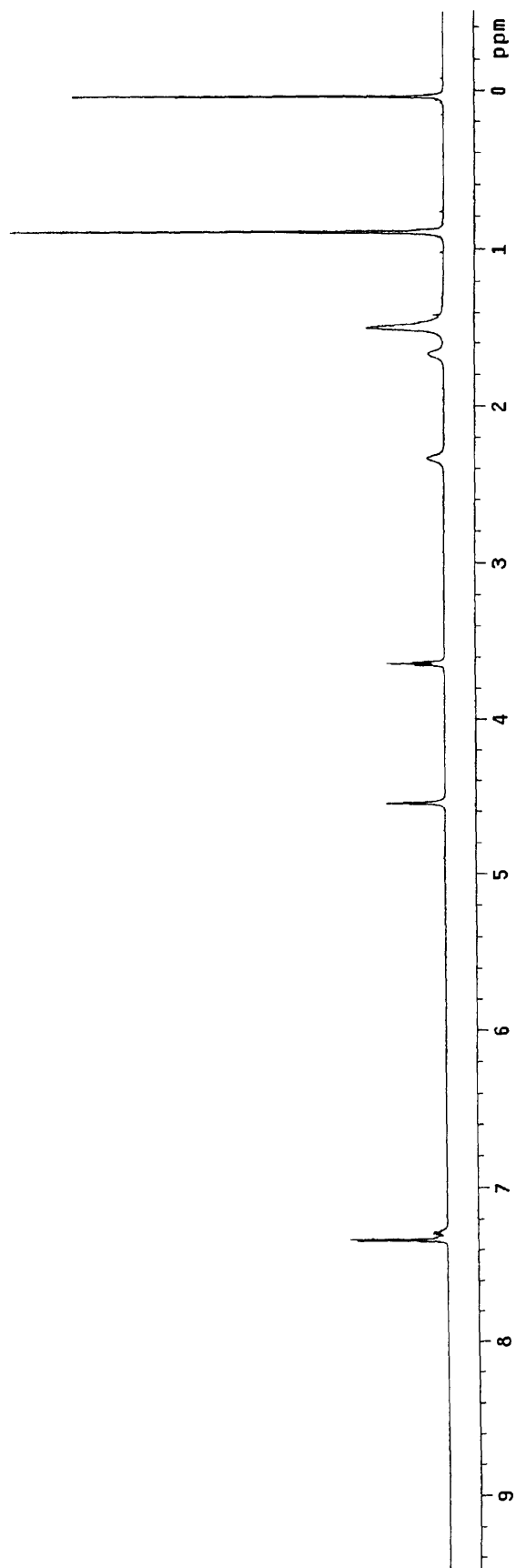
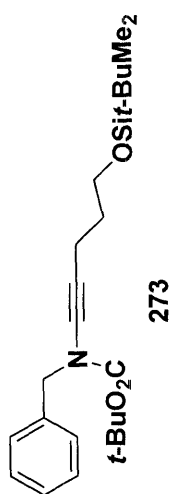
Reaction of a solution of carbamate **265** (0.189 g, 0.912 mmol) in 3.6 mL of pyridine with KHMDS (1.0 mL, 0.91 M in THF, 0.91 mmol), CuI (0.174 g, 0.914 mmol) in 2.8 mL of pyridine, and 1-bromo-2-phenylacetylene (**224**) (3.0 mL, 0.60 M in benzene, 1.8 mmol) according to the general procedure gave 0.457 g of a dark red oil. Column chromatography on 50 g of silica gel (elution with benzene) provided 0.171 g (61%) of ynamide **272** as an orange oil: IR (neat): 3033, 2979, 2242, 1721, 1600, 1496, 1454, 1393, 1369, 1301, 1242, and 1155 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.49 (m, 2H), 7.43 (m, 2H), 7.38 (m, 3H), 7.32 (m, 2H), 7.28 (m, 1H), 4.74 (s, 2H), and 1.60 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 153.9, 136.5, 130.6, 128.6, 128.4, 128.3, 128.0, 127.2, 123.7, 84.2, 82.7, 71.2, 53.1, and 28.1; HRMS-ESI *m/z*: [M+Na]⁺ calcd for C₂₀H₂₁NO₂, 330.1465; found, 330.1452.

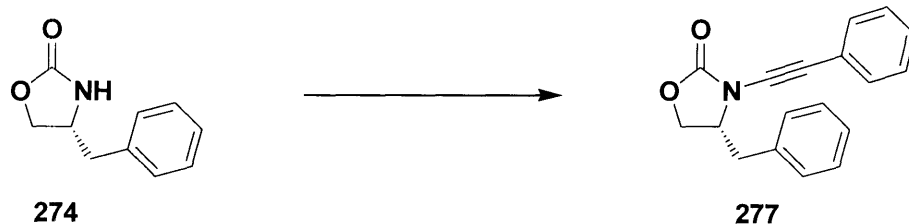




***N*-Benzyl-*N*-*tert*-butoxycarbonyl-5-(*tert*-butyldimethylsiloxy)-1-pentynylamine (**273**).**

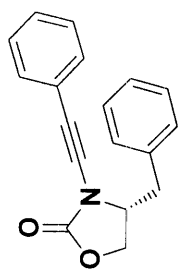
Reaction of a solution of carbamate **265** (0.207 g, 0.999 mmol) in 4.0 mL of pyridine with KHMDS (1.1 mL, 0.91 M in THF, 1.0 mmol), CuI (0.191 g, 1.00 mmol) in 3.0 mL of pyridine, and 1-bromo-5-(*t*-butyldimethylsiloxy)-1-pentyne (**229**) (3.3 mL, 0.60 M in benzene, 2.0 mmol) according to the general procedure gave 0.706 g of a dark red oil. Column chromatography on 40 g of silica gel (gradient elution with 0.5–2% EtOAc-hexanes) provided 0.213 g (53%) of ynamide **273** as a yellow oil: IR (neat): 3033, 2954, 2929, 2857, 2264, 1720, 1606, 1497, 1471, 1455, 1391, 1368, 1295, 1256, 1162, 1105, and 836 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.33 (app d, *J* = 4.6 Hz, 2H), 7.29 (m, 3H), 4.54 (s, 2H), 3.64 (t, *J* = 6.1 Hz, 2H), 2.33 (m, 2H), 1.66 (m, 2H), 1.48 (br s, 9H), 0.90 (s, 9H), and 0.04 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 154.7, 137.0, 128.5, 128.2, 127.7, 82.1, 74.7, 69.4, 61.6, 53.0, 32.2, 28.2, 26.0, 18.4, 15.0, and -5.2; HRMS-ESI *m/z*: [M+Na]⁺ calcd for C₂₃H₃₇NO₃Si, 426.2435; found, 426.2425.



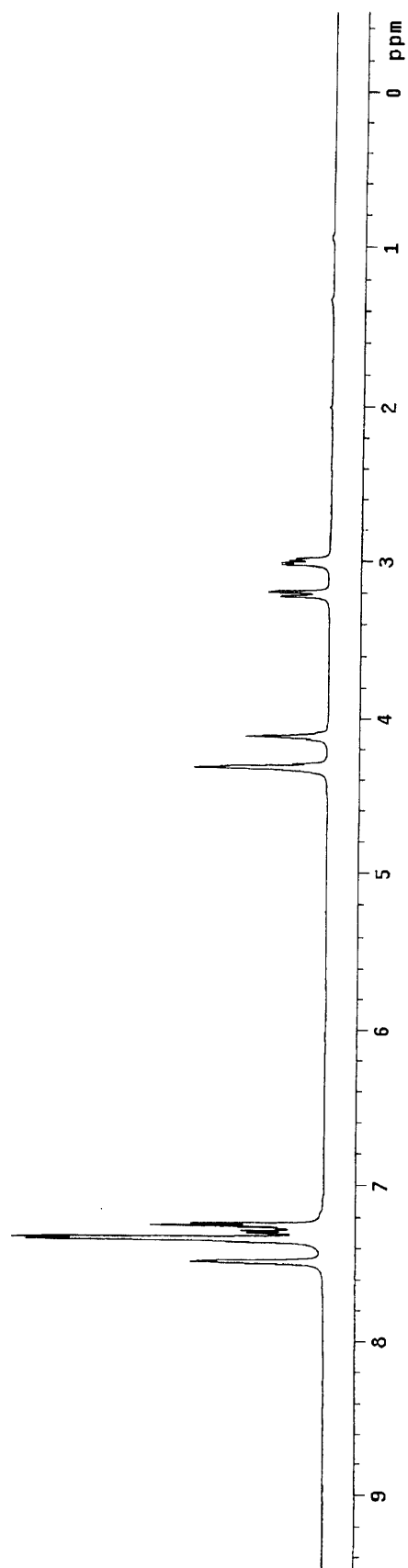


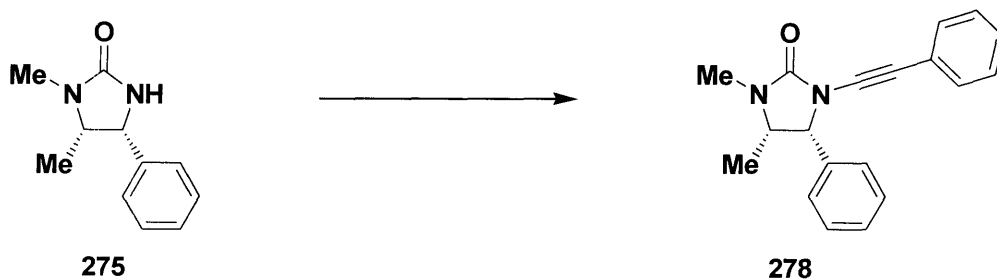
(R)-(+)-4-Benzyl-3-(2-phenylethynyl)-2-oxazolidinone (277).

Reaction of a solution of oxazolidinone **274** (0.225 g, 1.27 mmol) in 5.1 mL of pyridine with KHMDS (1.4 mL, 0.91 M in THF, 1.3 mmol), CuI (0.243 g, 1.28 mmol) in 3.6 mL of pyridine, and 1-bromo-2-phenylacetylene (**224**) (4.2 mL, 0.60 M in benzene, 2.5 mmol) according to the general procedure gave 0.555 g of a dark red oil. Column chromatography on 40 g of silica gel (gradient elution with 0–10% EtOAc-hexanes) provided 0.262 g (74%) of ynamide **277** as a light tan solid: mp 87–88 °C; IR (CH₂Cl₂): 3060, 3029, 2917, 2256, 1777, 1602, 1497, 1476, 1454, 1442, 1411, 1285, 1210, 1158, and 1088 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.49 (m, 2H), 7.24–7.36 (m, 8H), 4.31 (m, 2H), 4.12 (m, 1H), 3.21 (m, 1H), and 3.00 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 155.4, 134.2, 131.4, 129.3, 128.8, 128.2, 128.1, 127.3, 122.1, 78.2, 73.0, 67.3, 58.1, and 37.6; HRMS-EI *m/z*: [M]⁺ calcd for C₁₈H₁₅NO₂, 277.1097; found, 277.1107.



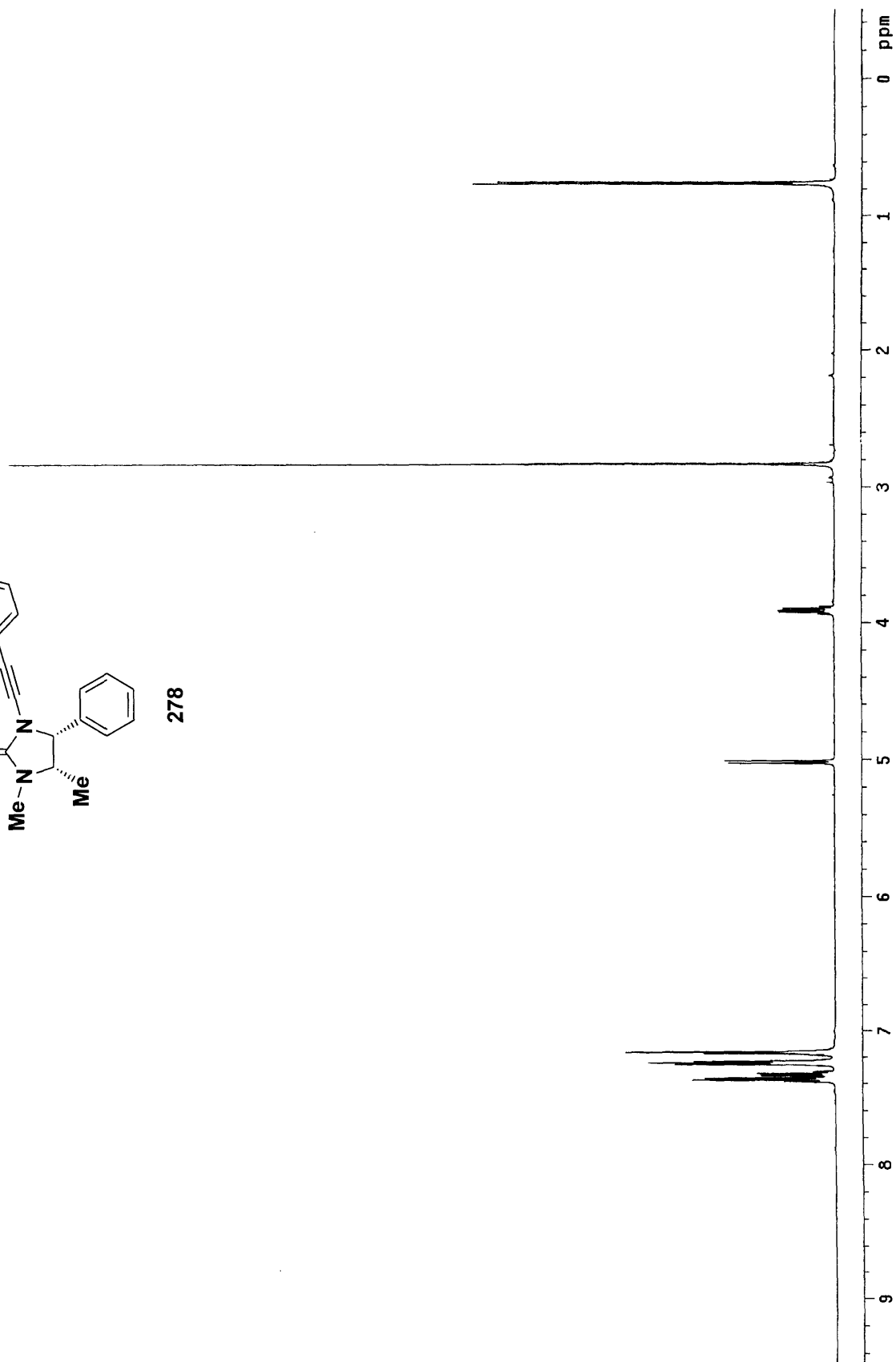
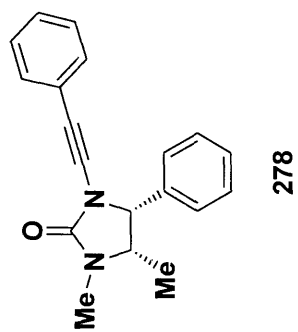
277

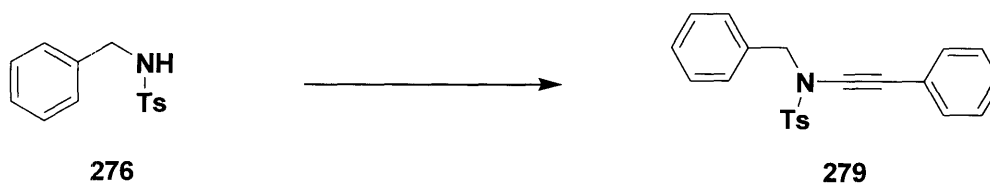




(4*R*,5*S*)-(-)-1,5-Dimethyl-4-phenyl-3-(2-phenylethynyl)-2-imidazolidinone (278).

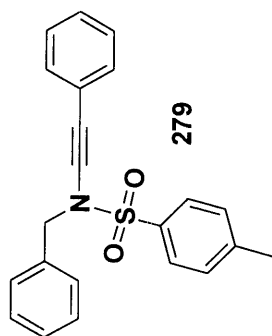
Reaction of a solution of imidazolidinone **275** (0.242 g, 1.27 mmol) in 5.0 mL of pyridine with KHMDS (1.4 mL, 0.91 M in THF, 1.3 mmol), CuI (0.243 g, 1.28 mmol) in 3.5 mL of pyridine, and 1-bromo-2-phenylacetylene (**224**) (4.2 mL, 0.60 M in benzene, 2.5 mmol) according to the general procedure gave 0.563 g of a dark red solid. Column chromatography on 40 g of silica gel (gradient elution with 0–30% EtOAc-hexanes) provided 0.222 g (60%) of ynamide **278** as a light purple solid: mp 187–188 °C; IR (CH₂Cl₂): 3054, 2986, 2240, 1726, 1599, 1441, 1403, 1265, 1167, 896, and 739 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.31–7.39 (m, 3H), 7.24 (m, 4H), 7.17 (m, 3H), 5.02 (d, *J* = 8.9 Hz, 1H), 3.91 (dq, *J* = 6.6, 8.9 Hz, 1H), 2.83 (s, 3H), and 0.76 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 157.6, 134.7, 131.2, 128.5, 128.5, 128.0, 127.7, 127.2, 123.4, 81.7, 71.4, 64.1, 55.6, 28.9, and 14.8; HRMS-ESI *m/z*: [M+H]⁺ calcd for C₁₉H₁₈N₂O, 291.1492; found, 291.1490.



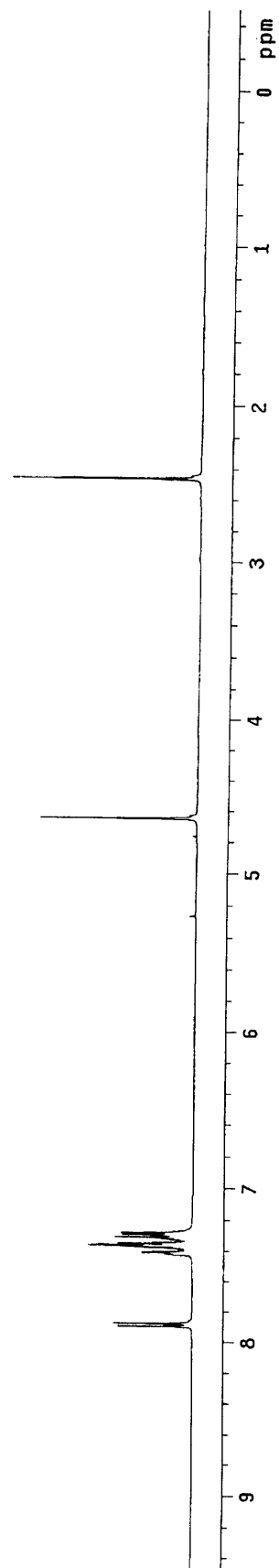


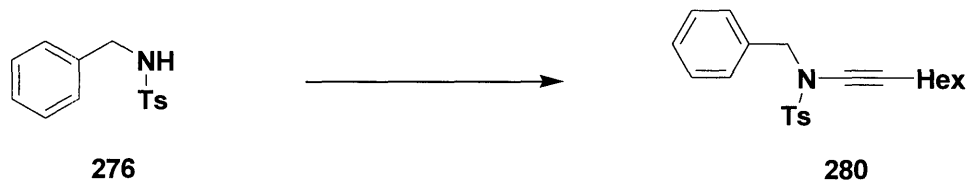
***N*-Benzyl-*N*-(2-phenylethynyl)-*p*-toluenesulfonamide (**279**).**

Reaction of a solution of sulfonamide **276** (0.268 g, 1.03 mmol) in 4.1 mL of pyridine with KHMDS (1.1 mL, 0.91 M in THF, 1.0 mmol), CuI (0.197 g, 1.03 mmol) in 3.1 mL of pyridine, and 1-bromo-2-phenylacetylene (**224**) (3.4 mL, 0.60 M in benzene, 2.0 mmol) according to the general procedure gave 0.561 g of a dark red oil. Column chromatography on 35 g of silica gel (gradient elution with 0–10% EtOAc-hexanes) provided 0.291 g (78%) of ynamide **279** as a pale yellow solid: mp 82–83 °C; IR (CH₂Cl₂): 3035, 2928, 2235, 1598, 1495, 1456, 1443, 1366, 1171, and 1090 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.89 (d, *J* = 8.2 Hz, 2H), 7.41 (m, 2H), 7.36 (m, 5H), 7.28–7.33 (m, 5H), 4.65 (s, 2H), and 2.46 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 144.8, 134.5, 134.4, 131.1, 129.8, 128.9, 128.5, 128.4, 128.2, 127.7, 127.7, 122.7, 82.7, 71.4, 55.7, and 21.6; HRMS-EI *m/z*: [*M*]⁺ calcd for C₂₂H₁₉NO₂S, 361.1131; found, 361.1135.



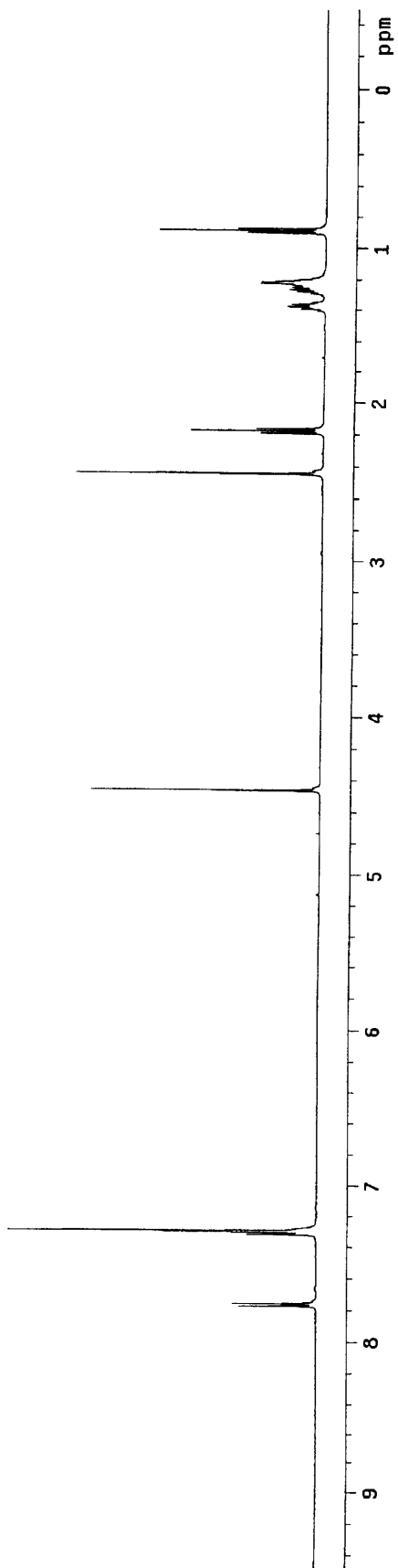
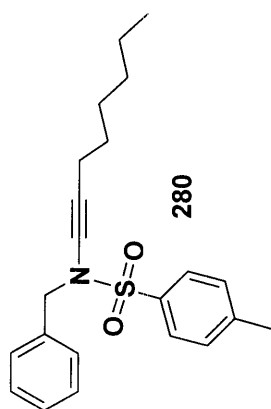
279

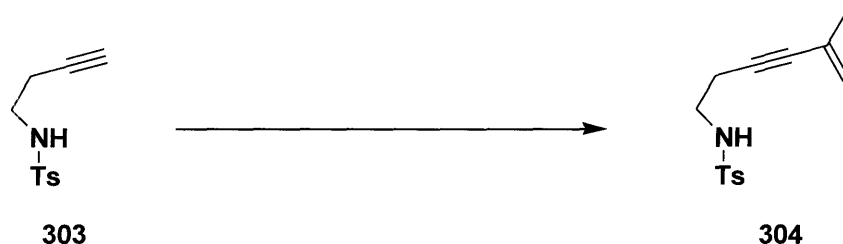




***N*-Benzyl-*N*-(1-octynyl)-*p*-toluenesulfonamide (**280**).**

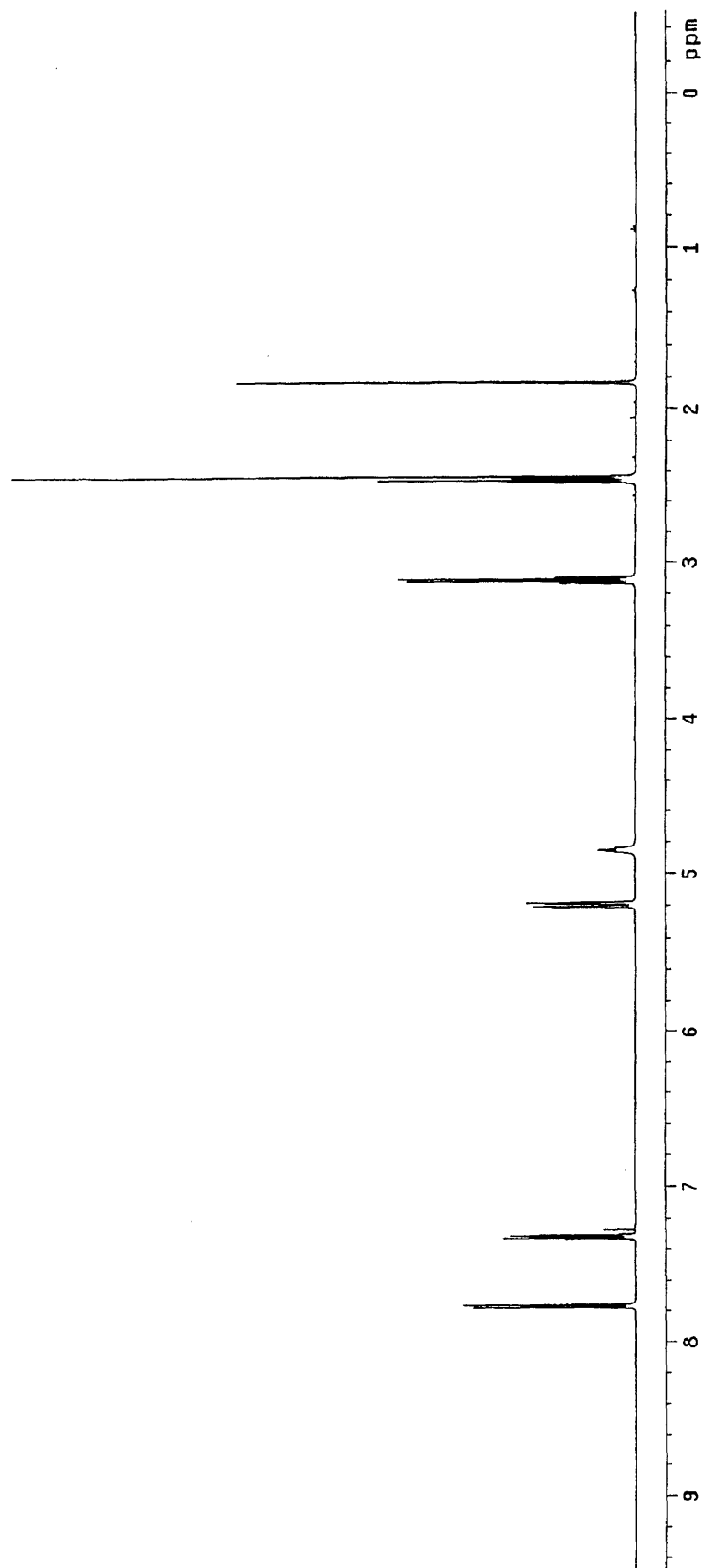
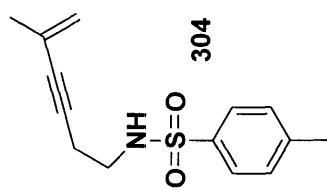
Reaction of a solution of sulfonamide **276** (0.260 g, 0.995 mmol) in 4.0 mL of pyridine with KHMDS (1.1 mL, 0.91 M in THF, 1.0 mmol), CuI (0.191 g, 1.00 mmol) in 3.0 mL of pyridine, and 1-bromo-1-octyne (**227**) (3.3 mL, 0.60 M in benzene, 2.0 mmol) according to the general procedure gave 0.453 g of a dark red oil. Column chromatography on 35 g of silica gel (gradient elution with 0–5% EtOAc-hexanes) provided 0.155 g (42%) of ynamide **280** as a yellow oil: IR (neat): 3033, 2930, 2858, 2254, 1597, 1497, 1455, 1365, 1169, 1091 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.77 (d, $J = 8.2$ Hz, 2H), 7.31 (d, $J = 8.2$ Hz, 2H), 7.29 (m, 5H), 4.46 (s, 2H), 2.44 (s, 3H), 2.18 (t, $J = 7.0$ Hz, 2H), 1.38 (app quartet, $J = 7.0$ Hz, 2H), 1.19–1.29 (m, 6H), and 0.89 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 144.4, 134.9, 134.7, 129.7, 128.8, 128.5, 128.2, 127.7, 73.4, 70.9, 55.6, 31.4, 28.8, 28.4, 22.6, 21.7, 18.4, and 14.2; HRMS-ESI m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{27}\text{NO}_2\text{S}$, 392.1655; found, 392.1645.

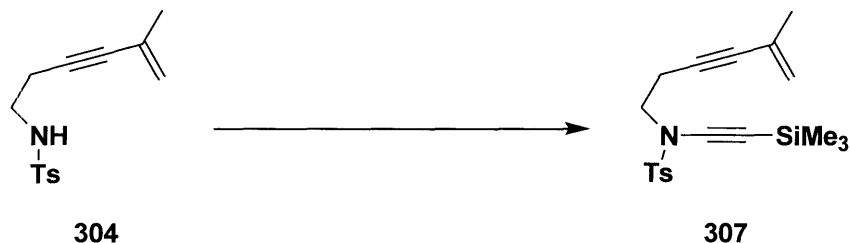




***N*-(5-Methyl-5-hexen-3-ynyl)-*p*-toluenesulfonamide (304).**

A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and reflux condenser fitted with an argon inlet adapter was charged with $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ (0.377 g, 0.537 mmol), CuI (0.204 g, 1.07 mmol), alkyne **303** (2.000 g, 8.957 mmol), and 15 mL of THF. 2-Bromopropene (2.4 mL, 3.3 g, 27 mmol) and piperidine (3.1 mL, 2.7 g, 31 mmol) were added sequentially via syringe, and the reaction mixture was heated at reflux for 90 min. The resulting suspension was allowed to cool to room temperature, diluted with 50 mL of Et_2O , and filtered through a 5 x 2.5 cm plug of silica gel with the aid of 300 mL of Et_2O . Concentration of the filtrate afforded 6.521 g of a brown oil. Column chromatography on 150 g of silica gel (gradient elution with 10–20% EtOAc-hexanes) provided 1.843 g (78%) of enyne **304** as a beige solid: mp 51–52 °C; IR (CHCl_3) 3384, 2953, 2258, 1613, 1599, 1410, 1334, and 1093 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.77 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 5.21 (s, 1H), 5.18 (s, 1H), 4.85 (t, J = 6.4 Hz, 1H), 3.11 (dt, J = 6.4, 6.7 Hz, 2H), 2.46 (t, J = 6.7 Hz, 2H), 2.43 (s, 3H), and 1.84 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 143.8, 137.1, 130.0, 127.3, 126.7, 122.0, 84.7, 84.3, 42.0, 23.8, 21.7, and 20.7; GC-MS m/z : 263 (M^+).

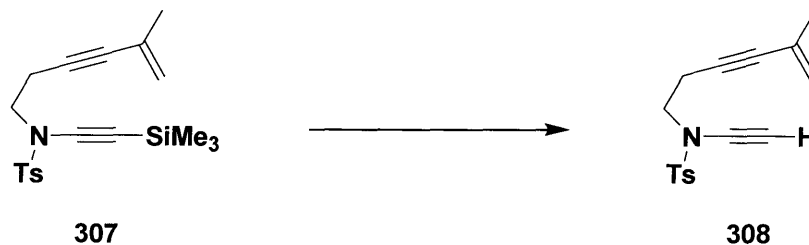




***N*-(5-Methyl-5-hexen-3-ynyl)-*N*-[2-(trimethylsilyl)ethynyl]-*p*-toluenesulfonamide (307).**

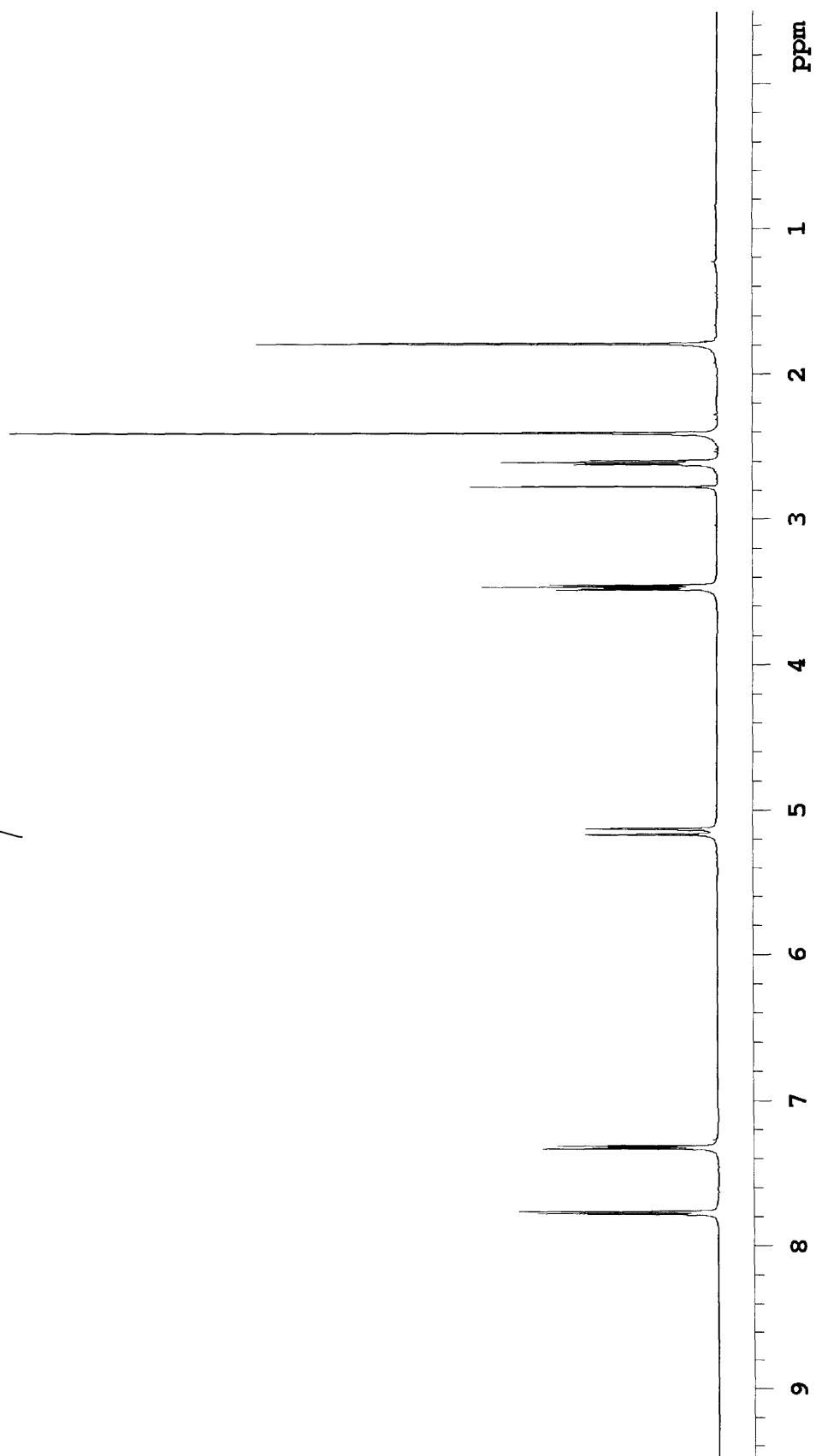
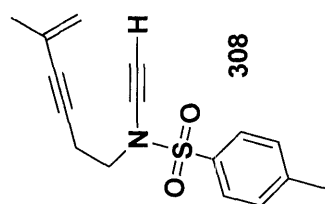
A 50-mL, pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with sulfonamide **304** (0.820 g, 3.11 mmol) and 30 mL of toluene. A solution of KHMDS (6.2 mL, 0.55 M in toluene, 3.4 mmol) was added via syringe over 5 min, and the resulting solution was stirred at rt for 1 h. A 250-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and argon inlet adapter was charged with [2-(trimethylsilyl)ethynyl](phenyl)iodonium triflate (**146c**) (1.680 g, 3.731 mmol) and 50 mL of toluene. The potassium sulfonamide solution was then added via cannula over 10 min (5-mL toluene rinse), and the resulting suspension was stirred at rt for 22 h. The reaction mixture was filtered through a 5 x 2.5 cm plug of silica gel with the aid of 500 mL of 20% EtOAc-hexanes, and then the filtrate was concentrated to provide 1.242 g of a brown oil. Column chromatography on 80 g of silica gel (elution with 5% EtOAc-hexanes) provided 0.868 g (78%) of ynamide **307** as a pale yellow oil: IR (CHCl₃) 2959, 2254, 2158, 1612, 1597, 1371, and 1092 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.80 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 5.21 (s, 1H), 5.17 (s, 1H), 3.50 (t, *J* = 7.8 Hz, 2H), 2.63 (t, *J* = 7.8 Hz, 2H), 2.46 (s, 3H), 1.84 (s, 3H), and 0.16 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 145.0, 134.6, 129.9, 127.9, 126.9, 121.7, 94.5, 84.4, 83.9, 73.8, 50.3, 23.7, 21.9, 19.3, and 0.3; GC-MS *m/z*: 359 (M⁺).





***N*-(5-Methyl-5-hexen-3-ynyl)-*N*-(ethynyl)-*p*-toluenesulfonamide (308).**

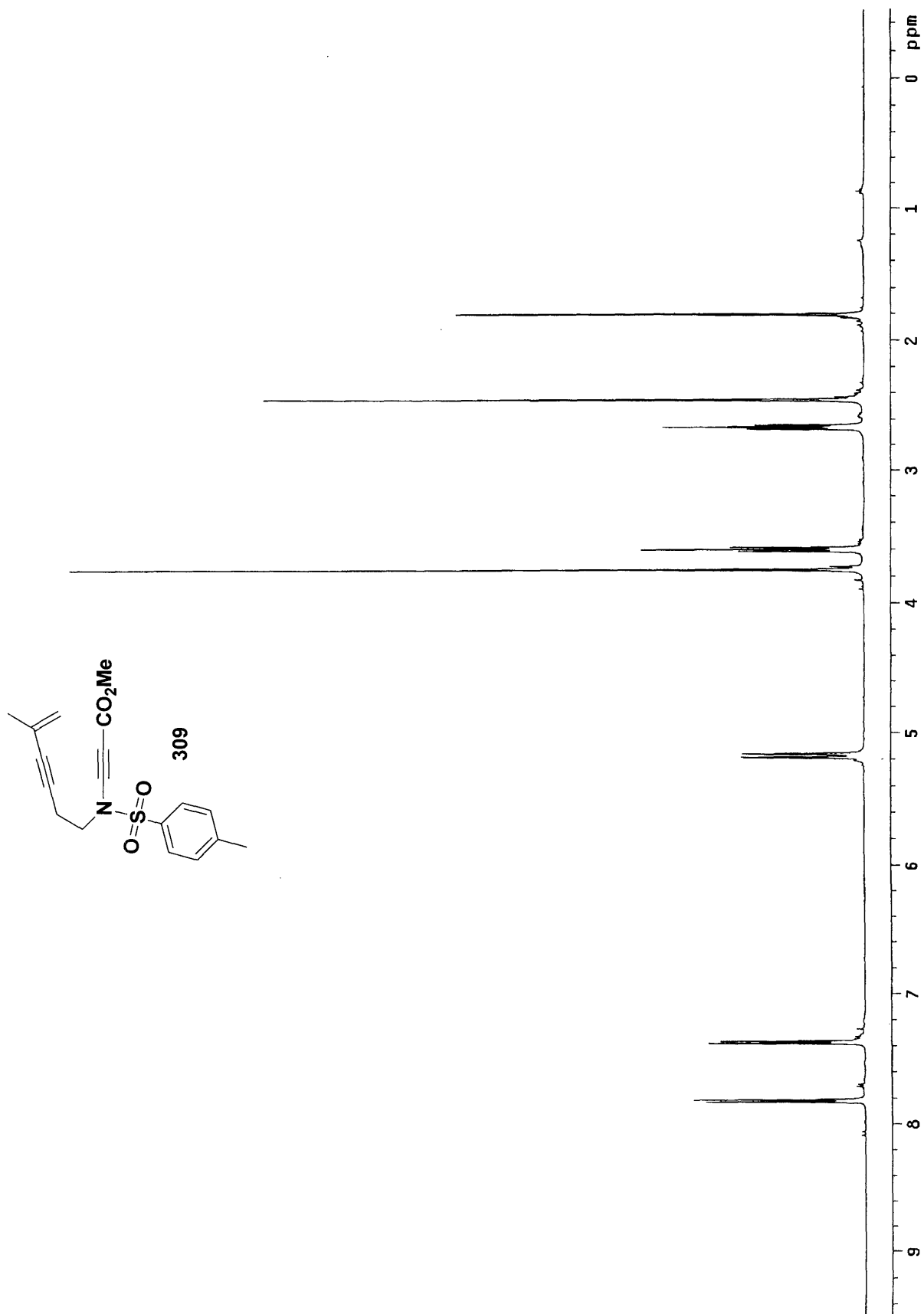
A 100-mL round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with ynamide **307** (0.235 g, 0.654 mmol) and 20 mL of THF. The solution was cooled at 0 °C while 0.85 mL of *n*-Bu₄NF solution (1.0 M in THF, 0.85 mmol) was added via syringe, and the resulting solution was stirred at 0 °C for 20 min. The reaction mixture was diluted with 20 mL of Et₂O, washed with 20 mL of satd NaCl solution, dried over MgSO₄, filtered, and concentrated to provide 0.356 g of a dark red oil. Column chromatography on 30 g silica gel (elution with 5% EtOAc-hexanes) provided 0.156 g (83%) of ynamide **308** as a pale yellow oil: IR (neat) 3293, 2922, 2230, 2139, 1613, 1596, 1450, 1369, and 1092 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.80 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 5.20 (s, 1H), 5.16 (s, 1H), 3.50 (t, *J* = 7.7 Hz, 2H), 2.79 (s, 1H), 2.65 (t, *J* = 7.7 Hz, 2H), 2.45 (s, 3H), and 1.83 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 145.0, 134.5, 129.9, 127.6, 126.6, 121.5, 84.1, 83.8, 75.5, 59.7, 50.0, 23.5, 21.6, and 19.1; GC-MS *m/z*: 287 (M⁺).

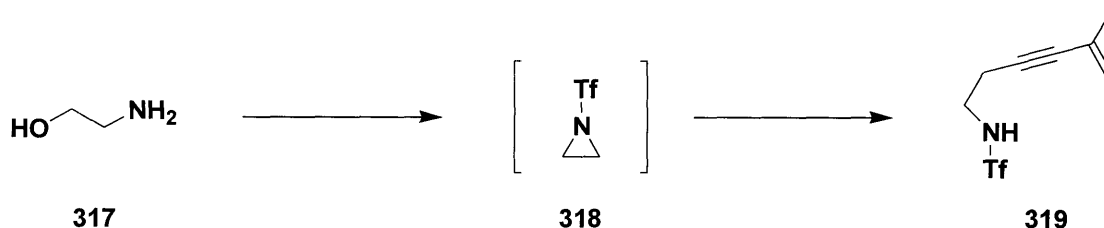




***N*-[2-(Methoxycarbonyl)ethynyl]-*N*-(5-methyl-5-hexen-3-ynyl)-*p*-toluenesulfonamide (**309**).**

A 10-mL pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with a sodium hydride dispersion (60% in mineral oil, 0.020 g, 0.49 mmol) and 1.1 mL of DMF. A solution of sulfonamide **304** (0.099 g, 0.38 mmol) in 1.3 mL of DMF was added via cannula over 2 min (0.4-mL DMF rinse) and the resulting slurry became homogeneous as it was allowed to stir at rt for 80 min. A 25-mL, two-necked, round-bottomed flask equipped with septum and argon inlet adapter was charged with methyl 3-bromopropiolate (**226**) (0.110 g, 0.68 mmol) and 0.6 mL of DMF. The solution was cooled at 0 °C while the previously prepared solution of sodium sulfonamide was added via cannula over 5 min (0.5-mL DMF rinse). The reaction flask was wrapped in aluminum foil to protect from light and the dark red solution was allowed to stir at 0 °C for 70 h. The cooled reaction mixture was diluted with 75 mL of Et₂O and 50 mL of ice-cold water, the aqueous phase was separated and extracted with twelve 75-mL portions of Et₂O, and the combined organic layers were washed with 100 mL of satd NaCl solution, dried over MgSO₄, filtered, and concentrated to provide 0.171 g of a brown oil. Column chromatography on 6 g of acetone-deactivated silica gel (elution with 5% EtOAc-hexanes) provided 0.071 g (54%) of ynamide **309** as a yellow oil: IR (CH₂Cl₂) 2955, 2220, 1709, 1597, 1439, 1376, and 1174 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.82 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 5.19 (s, 1H), 5.16 (s, 1H), 3.75 (s, 3H), 3.60 (t, *J* = 7.3 Hz, 2H), 2.66 (t, *J* = 7.3 Hz, 2H), 2.45 (s, 3H), and 1.81 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 154.5, 145.9, 134.3, 130.3, 127.9, 126.7, 121.8, 84.4, 83.5, 82.5, 67.8, 52.5, 50.3, 23.5, 21.9, and 19.7; GC-MS *m/z*: 345 (M⁺).



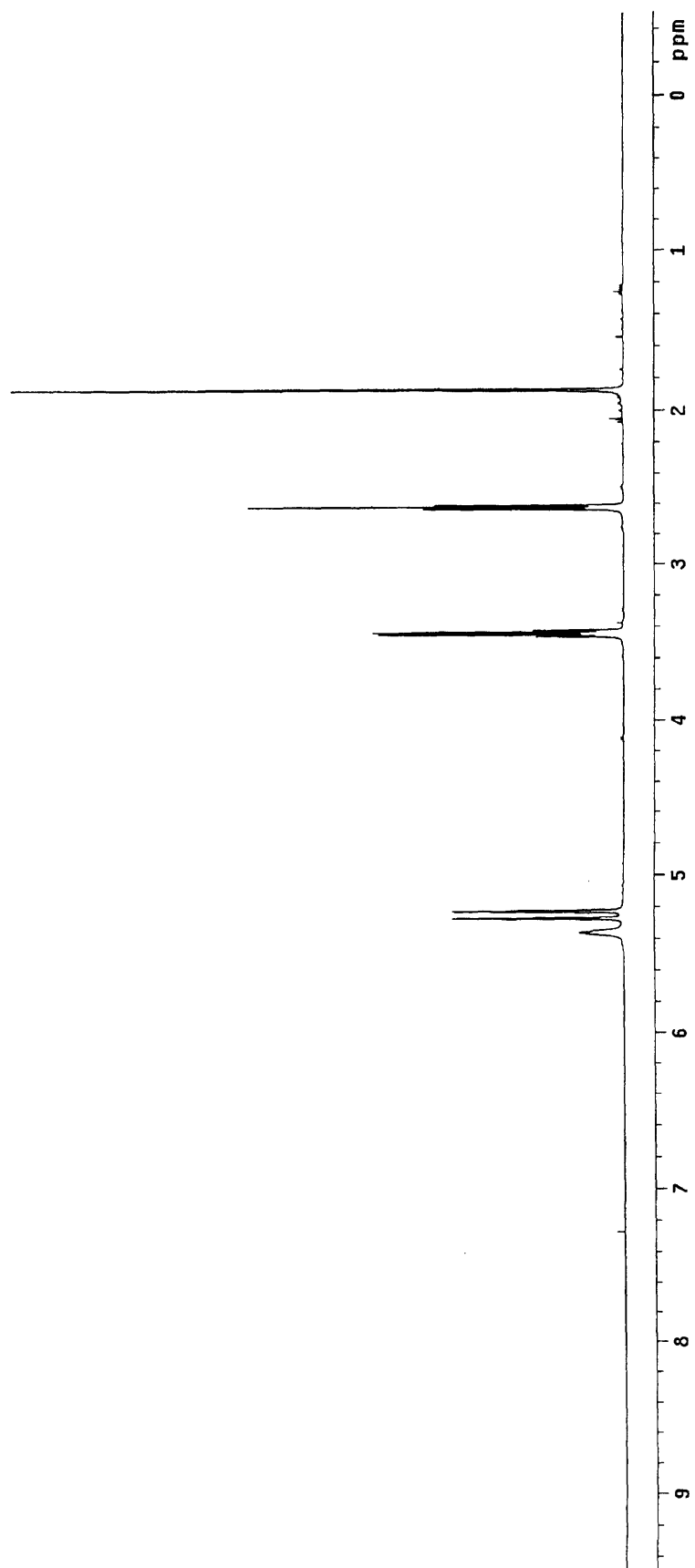
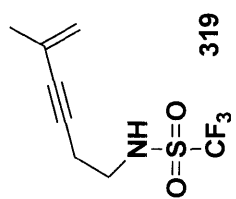


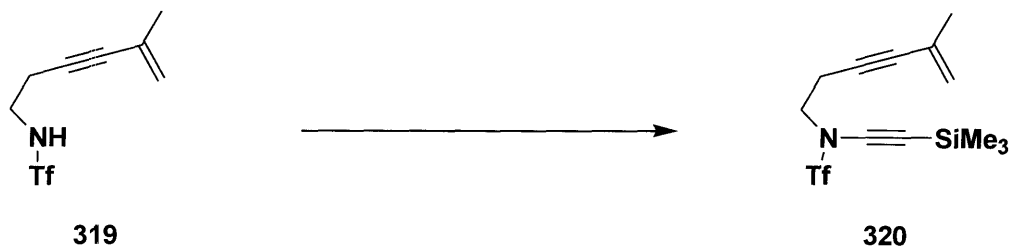
***N*-(5-Methyl-5-hexen-3-ynyl)trifluoromethanesulfonamide (**319**).**

A 500-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with 2-aminoethanol (**317**) (1.66 mL, 1.68 g, 27.5 mmol), 180 mL of CH₂Cl₂, and triethylamine (7.7 mL, 5.6 g, 55 mmol). The solution was cooled at –78 °C while triflic anhydride (10.0 mL, 16.8 g, 59.4 mmol) was added dropwise via syringe over 40 min. The resulting mixture was stirred at –78 °C for 2 h, allowed to warm to –25 °C, and then stirred at –25 °C for 15 h. The solution was diluted with 150 mL of CH₂Cl₂, washed with two 150-mL portions of ice-cold 0.1 N HCl and two 150-mL portions of ice-cold satd NaHCO₃ solution, dried over MgSO₄, filtered, and then diluted with 20 mL of THF. The resulting solution of aziridine **318** was concentrated to a volume of ca. 20 mL, diluted with another 20 mL portion of THF, and again concentrated to a volume of ca. 20 mL. This process was repeated two more times to remove CH₂Cl₂. The final solution of aziridine **318** in 40 mL of THF was dried over 3Å sieves for 1 h before use in the next step.

A 300-mL round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with 2-methyl-1-buten-3-yne (3.1 mL, 2.2 g, 33 mmol) and 70 mL of THF. The solution was cooled at –30 °C while 14.0 mL of *n*-BuLi solution (2.21 M in hexanes, 30.9 mmol) was added via syringe over 10 min. The resulting solution was stirred at –30 °C for 15 min and then the solution of aziridine **318** was added via cannula over 7 min (5-mL THF rinse). The resulting mixture was stirred at –30 °C for 20 h and then allowed to warm to room temperature. The reaction mixture was diluted with 50 mL of satd NH₄Cl solution and 200 mL of CH₂Cl₂, and washed with 150 mL of 0.1 N HCl. The aqueous phase was extracted with three 100-mL portions of CH₂Cl₂, and the combined organic layers were washed with 150 mL of satd NaCl solution, dried over MgSO₄, filtered, and concentrated to provide 9.185 g of a dark red oil. Column chromatography on 250 g of silica gel (elution with 5% EtOAc-hexanes) provided 3.396 g (51% overall from **317**) of triflamide **319** as an orange oil: IR (CHCl₃) 3379, 2957, 2254, 1614, 1429, 1378, and 1074 cm^{–1}; ¹H NMR (500 MHz, CDCl₃) δ 5.36 (br s, 1H), 5.27 (s,

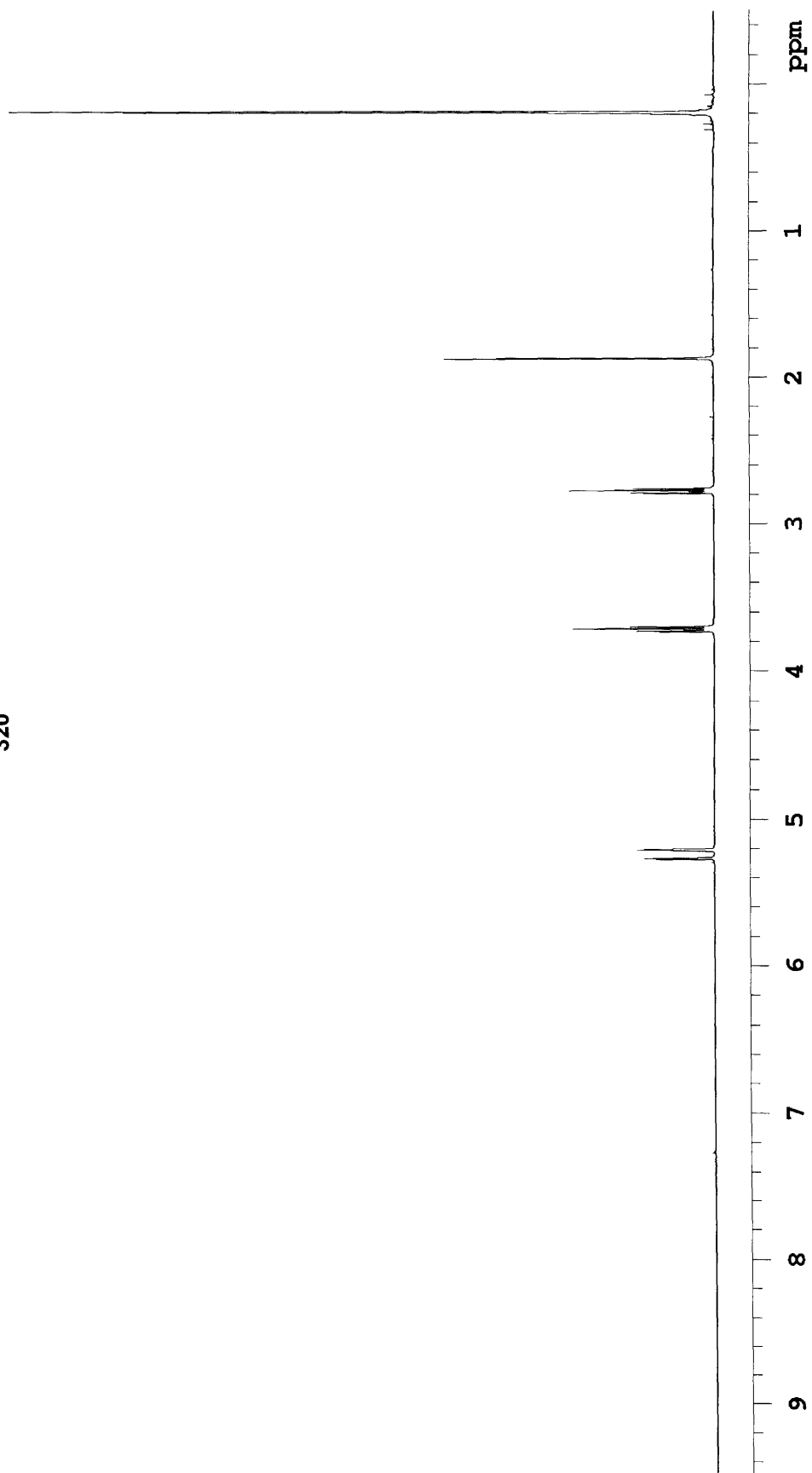
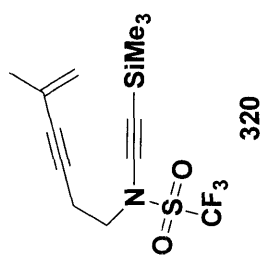
1H), 5.23 (s, 1H), 3.44 (app q, $J = 6.4$ Hz, 2H), 2.62 (t, $J = 6.4$ Hz, 2H), and 1.87 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 126.4, 122.2, 119.6 (q, $J_{\text{CF}} = 530$ Hz), 84.9, 83.5, 43.3, 23.7, and 21.6; GC-MS m/z : 241 (M^+).





***N*-(5-Methyl-5-hexen-3-ynyl)-*N*-[2-(trimethylsilyl)ethynyl]trifluoromethanesulfonamide (320).**

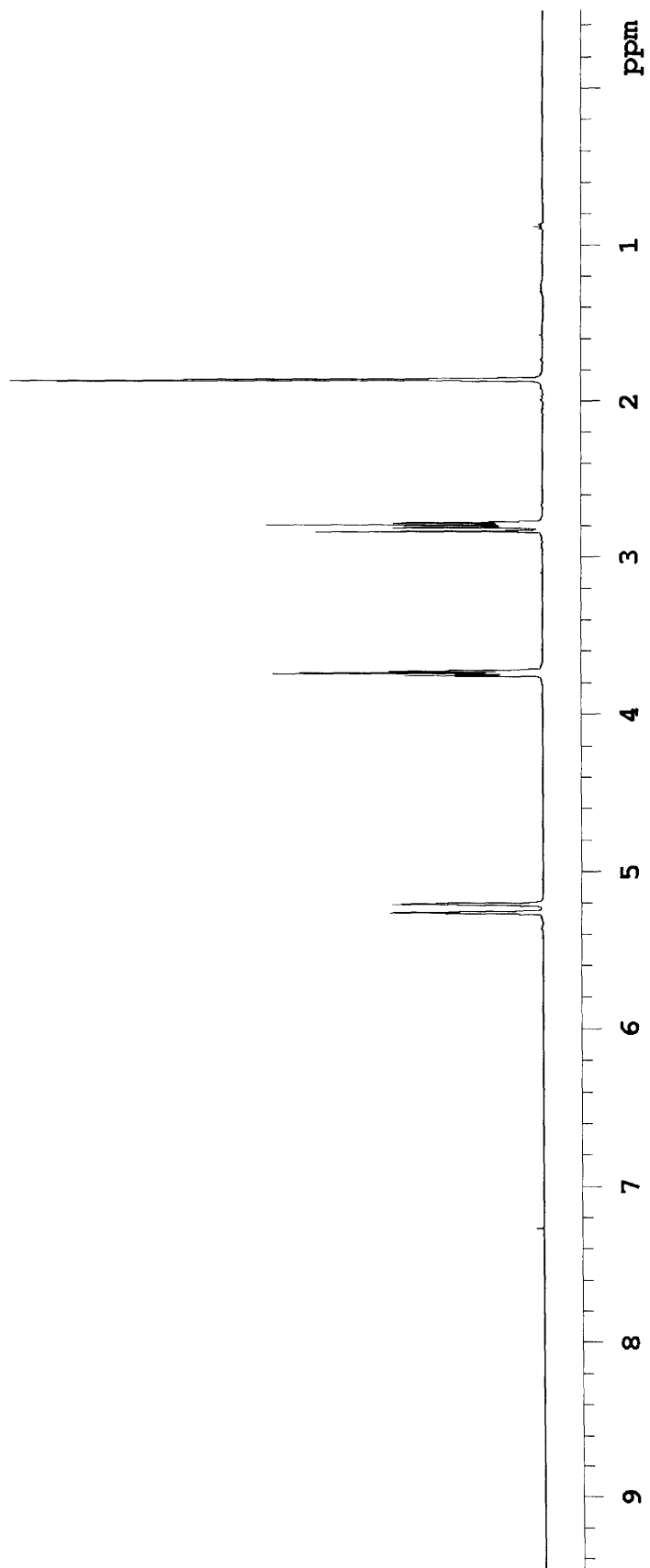
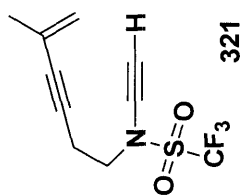
A 50-mL, pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with triflamide **319** (0.560 g, 2.32 mmol), 15 mL of toluene, and 5 mL of THF. A solution of KHMDS (4.6 mL, 0.55 M in toluene, 2.5 mmol) was added via syringe over 3 min, and the resulting solution was stirred at rt for 10 min. A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and argon inlet adapter was charged with [2-(trimethylsilyl)ethynyl](phenyl)iodonium triflate (**146c**) (1.250 g, 2.776 mmol) and 25 mL of toluene. The potassium triflamide solution was then added via cannula over 5 min, and the resulting suspension was stirred at rt for 24 h. The reaction mixture was diluted with 50 mL of CH₂Cl₂ and washed with 50 mL of satd NaCl solution. The aqueous layer was extracted with two 50-mL portions of CH₂Cl₂, and the combined organic layers were dried over MgSO₄, filtered, and concentrated to provide 1.252 g of a red oil. Column chromatography on 30 g of silica gel (gradient elution with 0–2% EtOAc-hexanes) provided 0.545 g (70%) of ynamide **320** as a pale yellow oil: IR (CHCl₃) 2961, 2254, 2186, 1614, 1414, and 1076 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.27 (s, 1H), 5.21 (s, 1H), 3.71 (t, *J* = 7.3 Hz, 2H), 2.77 (t, *J* = 7.3 Hz, 2H), 1.87 (s, 3H), and 0.19 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 126.7, 122.1, 119.9 (q, *J*_{CF} = 322 Hz), 89.7, 84.7, 82.9, 74.9, 52.2, 23.6, 19.4, and -0.1; GC-MS *m/z*: 337 (M⁺).

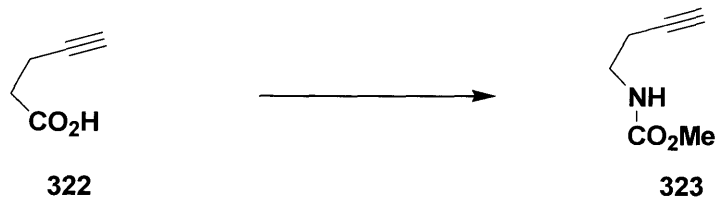




***N*-(5-Methyl-5-hexen-3-ynyl)-*N*-(ethynyl)trifluoromethanesulfonamide (**321**).**

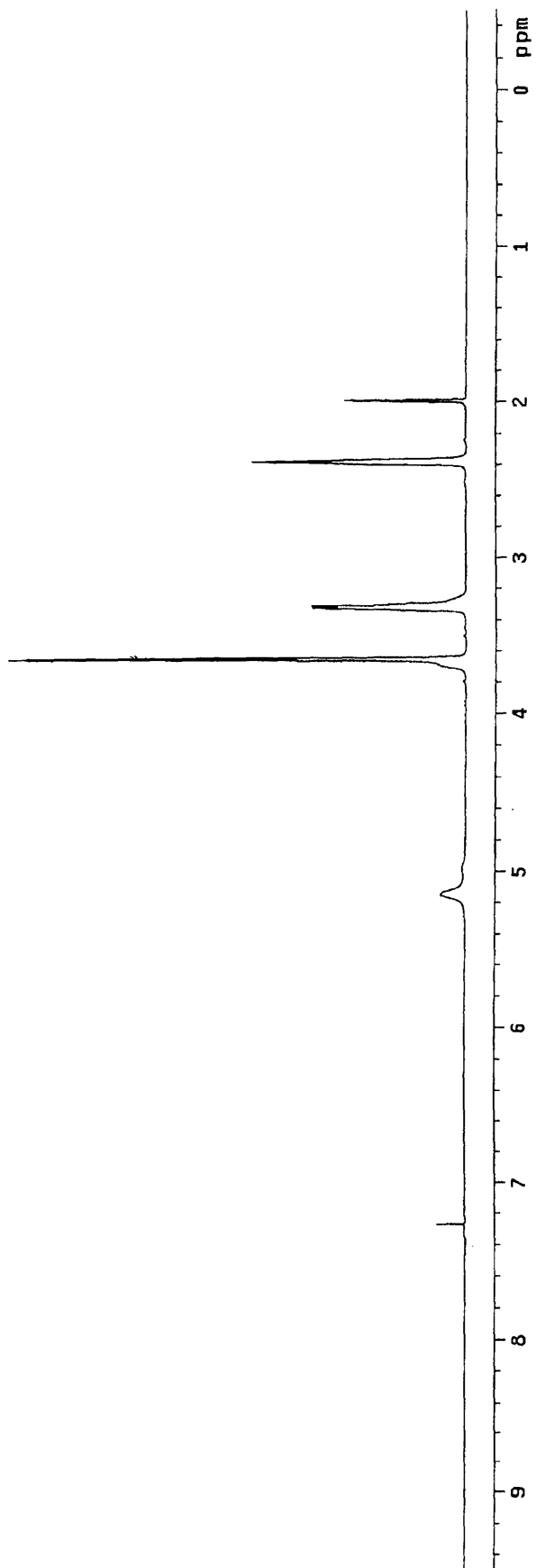
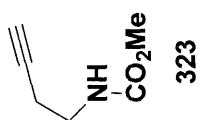
A 100-mL, three-necked, round-bottomed flask equipped with a glass stopper, two rubber septa, and an argon inlet needle was charged with triflamide **319** (0.460 g, 1.91 mmol), 19 mL of DMF, and Cs_2CO_3 (0.690 g, 2.12 mmol). A solution of [2-(trimethylsilyl)ethynyl](phenyl)iodonium triflate (**146c**) (1.040 g, 2.310 mmol) in 25 mL of CH_2Cl_2 was added via cannula in one portion (5-mL CH_2Cl_2 rinse), and the resulting solution was allowed to stir at rt for 16 h. The reaction mixture was then diluted with 200 mL of Et_2O and washed with four 200-mL portions of satd NaCl solution, dried over MgSO_4 , filtered, and concentrated to give 0.909 g of a pale brown oil. Column chromatography on 50 g of silica gel (elution with 2% EtOAc-hexanes) provided 0.437 g (87%) of ynamide **321** as a pale yellow oil: IR (CHCl_3) 3318, 2957, 2263, 2154, 1614, 1420, 1349, and 1077 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.26 (s, 1H), 5.21 (s, 1H), 3.74 (t, J = 7.2 Hz, 2H), 2.83 (s, 1H), 2.79 (t, J = 7.2 Hz, 2H), and 1.86 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 126.6, 122.0, 119.7 (q, J_{CF} = 322 Hz), 84.8, 82.7, 71.5, 60.3, 52.1, 23.5, and 19.4; GC-MS m/z : 265 (M^+).

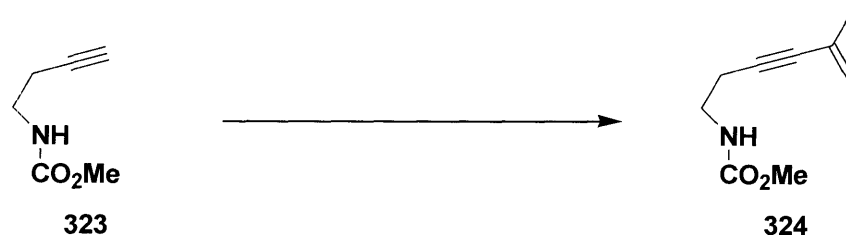




***N*-(Methoxycarbonyl)-3-butynylamine (323).**

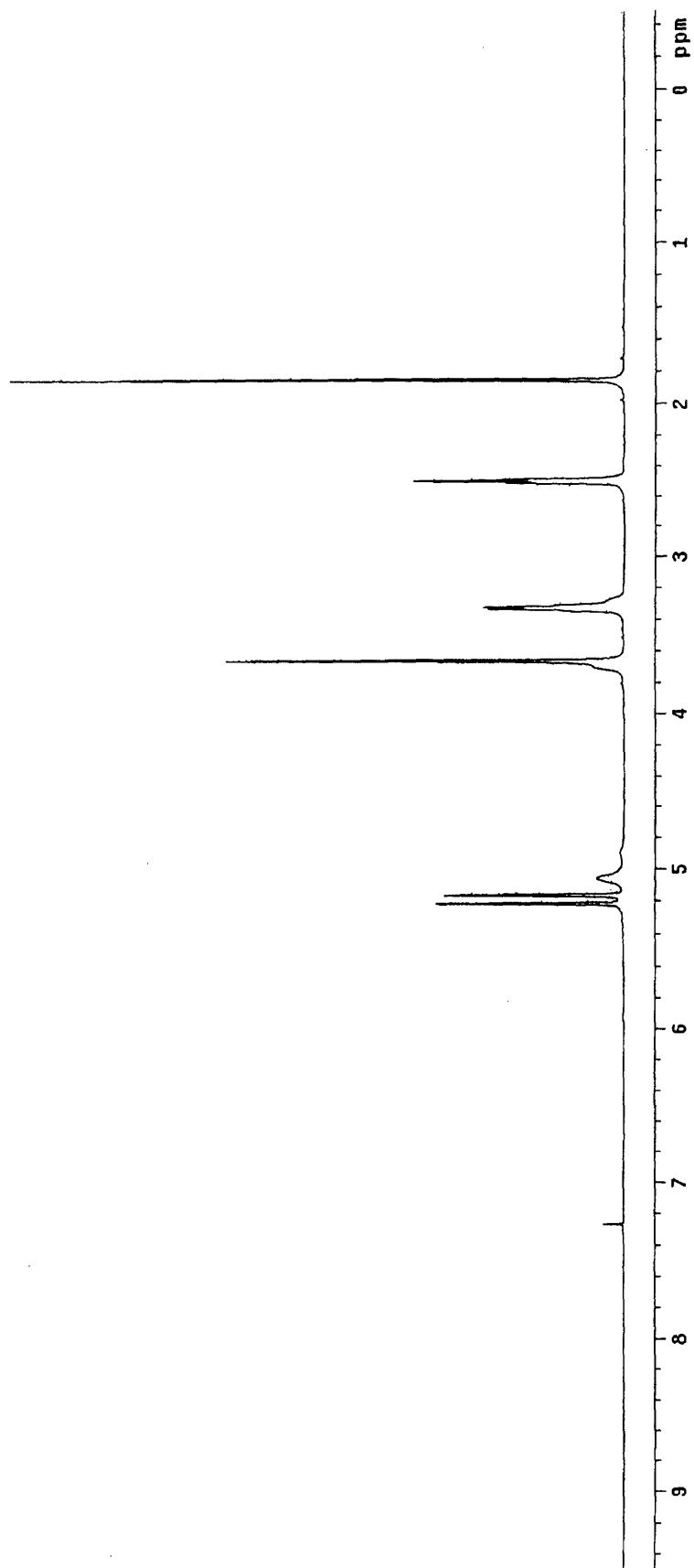
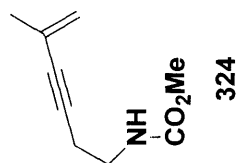
A 250-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and reflux condenser fitted with an argon inlet adapter was charged with 4-pentynoic acid (**322**) (5.174 g, 52.74 mmol), 75 mL of toluene, and triethylamine (7.4 mL, 5.4 g, 53 mmol). Diphenylphosphoryl azide (11.4 mL, 14.6 g, 52.9 mmol) was added via syringe over 5 min, and the resulting solution was heated at 80 °C (bath temperature) until bubbling ceased (2 h). The oil bath was cooled to 50 °C, methanol (22 mL, 17 g, 540 mmol) was added and the resulting mixture was stirred at 50 °C for 14 h. The reaction mixture was allowed to cool to room temperature and the toluene and methanol were removed by rotary evaporation at rt and 20 mmHg. The resulting yellow oil was diluted with 100 mL of Et₂O, 50 mL of water, and 10 mL of satd Na₂CO₃ solution. The aqueous layer was separated and extracted with ten 50-mL portions of Et₂O, and the combined organic layers were washed with 200 mL of satd NaCl solution, dried over MgSO₄, filtered, and concentrated to afford 7.102 g of a yellow oil. Column chromatography on 140 g of silica gel (gradient elution with 10–20% EtOAc-hexanes) provided 5.861 g (87%) of carbamate **323** as a pale yellow oil: IR (CH₂Cl₂) 3446, 3304, 2954, 2121, 1721, 1520, and 1469 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.02 and 5.17 (NH rotamers, br s, 1H), 3.64 (s, 3H), 3.31 (app q, *J* = 6.4 Hz, 2H), 2.37 (dt, *J* = 2.4, 6.4 Hz, 2H), and 1.99 (t, *J* = 2.4 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 157.0, 81.5, 70.0, 52.2, 39.7, and 19.9; GC-MS *m/z*: 127 (M⁺).

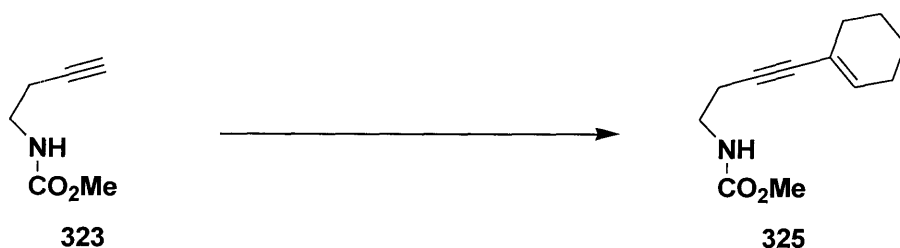




***N*-(Methoxycarbonyl)-5-methyl-5-hexen-3-ynamine (324).**

A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and reflux condenser fitted with an argon inlet adapter was charged with (Ph₃P)₂PdCl₂ (0.445 g, 0.634 mmol), CuI (0.234 g, 1.28 mmol), alkyne **323** (2.685 g, 21.12 mmol), and 35 mL of THF. 2-Bromopropene (2.8 mL, 3.8 g, 32 mmol) and piperidine (7.3 mL, 6.3 g, 74 mmol) were added sequentially via syringe, and the reaction mixture was heated at reflux for 5 h. The resulting suspension was allowed to cool to room temperature, diluted with 300 mL of Et₂O, and filtered through a 5 x 2.5 cm plug of silica gel with the aid of 400 mL of Et₂O. Concentration of the filtrate afforded 4.426 g of a brown oil. Column chromatography on 100 g of silica gel (elution with 10% EtOAc-hexanes) provided 2.972 g (84%) of enyne **324** as a pale brown oil: IR (neat) 3336, 2951, 2228, 1704, 1614, 1536, and 1450 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.21 (s, 1H), 5.16 (s, 1H), 4.90 and 5.06 (NH rotamers, br s, 1H), 3.66 (s, 3H), 3.32 (dt, *J* = 5.3, 5.8 Hz, 2H), 2.50 (t, *J* = 5.8 Hz, 2H), and 1.85 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 157.1, 127.0, 121.4, 86.0, 83.5, 52.3, 40.1, 23.8, and 20.9; GC-MS *m/z*: 167 (M⁺).

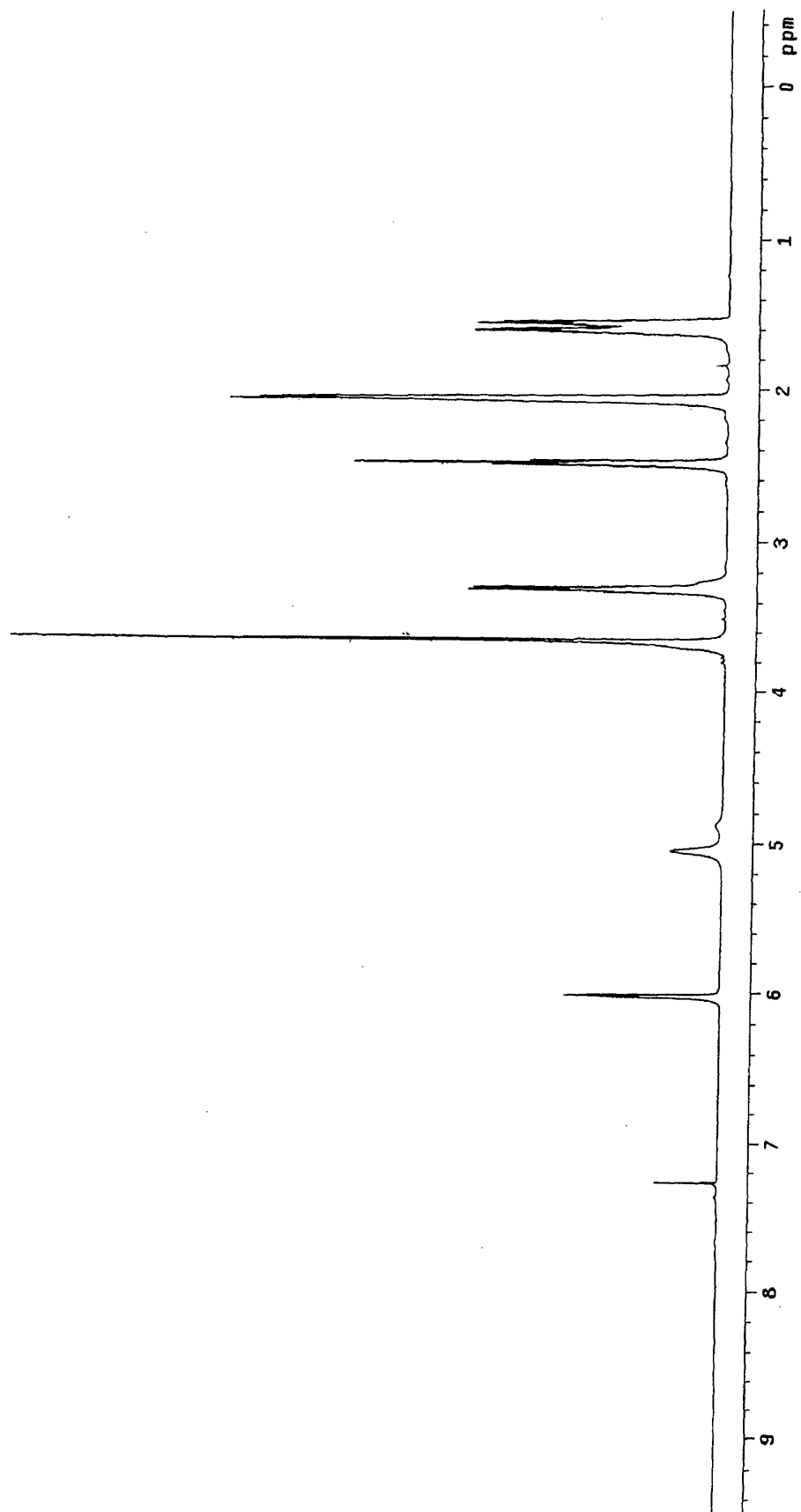
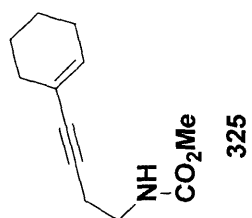


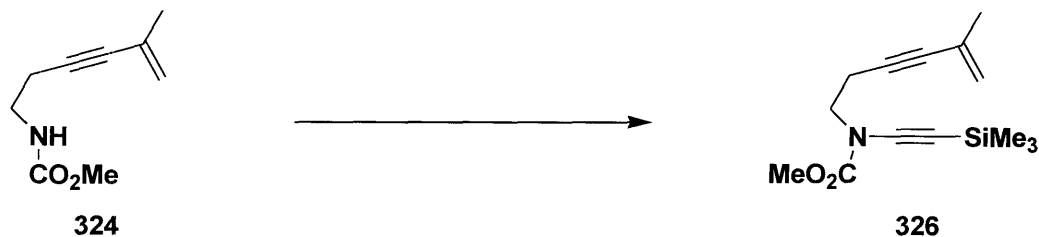


***N*-(Methoxycarbonyl)-4-(1-cyclohexenyl)-3-butynylamine (325).**

A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and argon inlet adapter was charged with $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ (0.233 g, 0.332 mmol), CuI (0.122 g, 0.641 mmol), and alkyne **323** (0.695 g, 5.47 mmol). A solution of 1-(trifluoromethanesulfonyl)cyclohexene²⁰² (8.6 mL, 1.0 M in THF, 8.6 mmol) was added, followed by piperidine (1.9 mL, 1.6 g, 19 mmol), and the resulting suspension was stirred at room temperature for 2 h. The reaction mixture was diluted with 100 mL of Et_2O and then filtered through a 5 x 2.5 cm plug of silica gel with the aid of 300 mL of Et_2O . Concentration of the filtrate afforded 2.051 g of a brown oil. Column chromatography on 120 g of silica gel (gradient elution with 0–10% EtOAc-hexanes) provided 0.852 g (75%) of enyne **325** as a yellow oil: IR (neat) 3336, 2932, 2223, 1707, 1536, and 1448 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.02 (m, 1H), 4.85 and 5.01 (NH rotamers, br s, 1H), 3.66 (s, 3H), 3.31 (app q, $J = 6.1$ Hz, 2H), 2.49 (t, $J = 6.1$ Hz, 2H), 2.04–2.09 (m, 4H), and 1.53–1.63 (m, 4H); ^{13}C NMR (125 MHz, CDCl_3) δ 157.0, 134.3, 120.7, 84.1, 83.9, 52.3, 40.2, 29.6, 25.7, 22.5, 21.7, and 20.9; HRMS-ESI m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{12}\text{H}_{17}\text{NO}_2$, 230.1151; found, 230.1153.

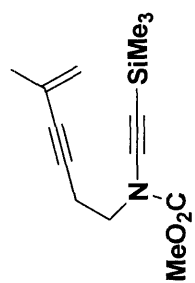
²⁰² Prepared according to the procedure of Stang, P. J.; Treptow, W. *Synthesis* **1980**, 283.



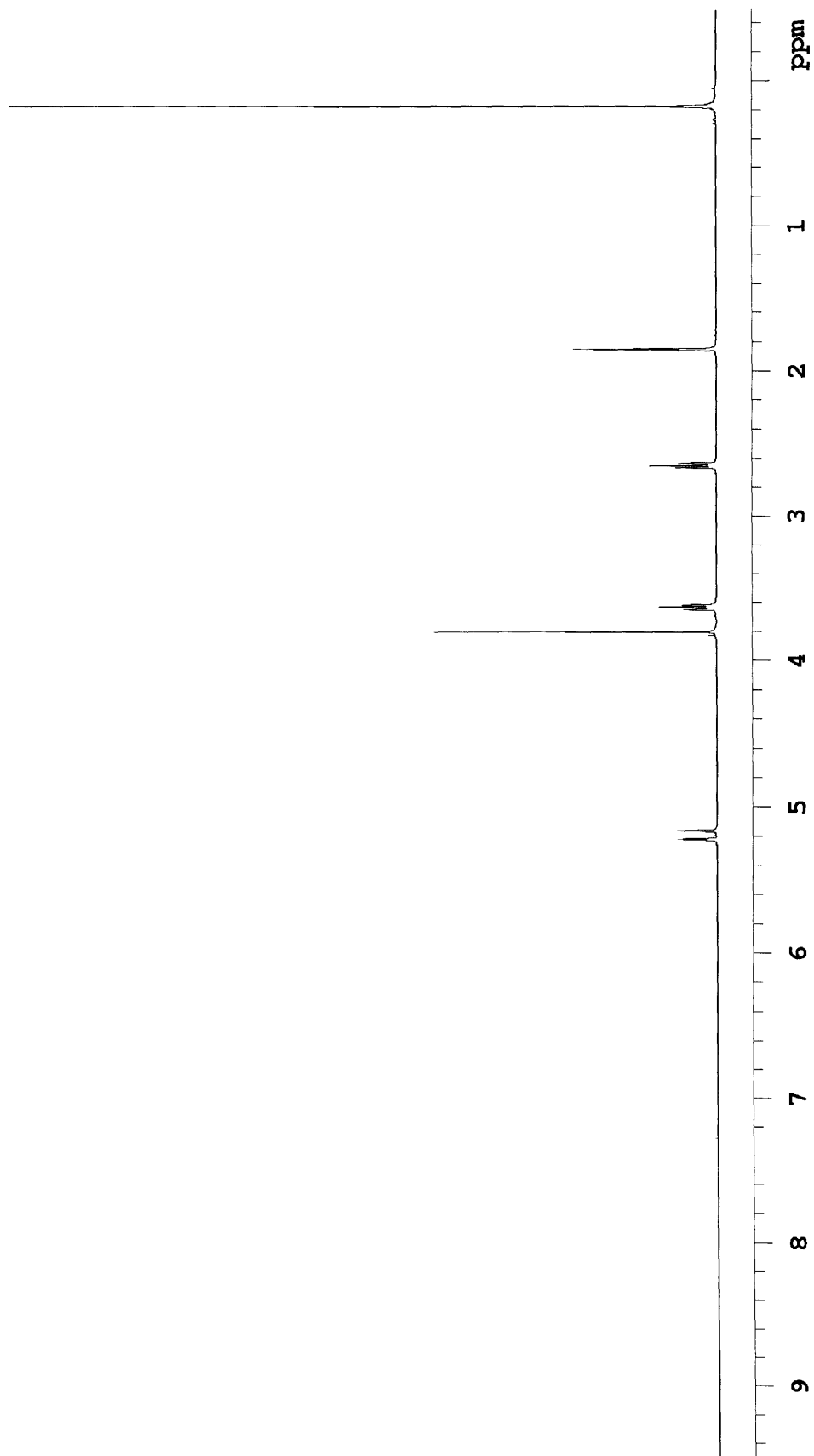


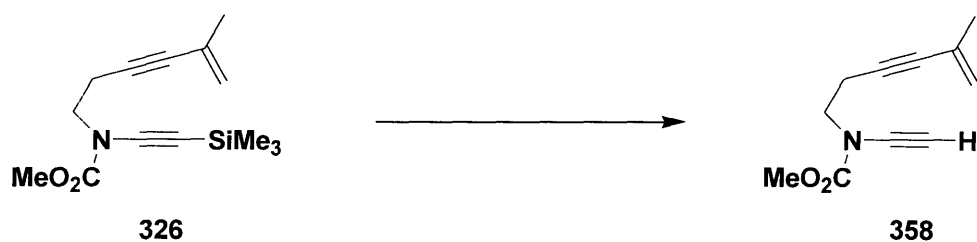
***N*-(Methoxycarbonyl)-*N*-[2-(trimethylsilyl)ethynyl]-5-methyl-5-hexen-3-ynylamine (**326**).**

Reaction of a solution of carbamate **324** (0.700 g, 4.19 mmol) in 17 mL of pyridine with KHMDS (4.6 mL, 0.91 M in THF, 4.2 mmol), CuI (0.799 g, 4.20 mmol) in 9 mL of pyridine, and 1-bromo-2-(trimethylsilyl)acetylene (**241**) (14 mL, 0.60 M in benzene, 8.4 mmol) according to the general procedure gave 1.458 g of a dark brown oil. Column chromatography on 80 g of silica gel (gradient elution with 0–3% EtOAc-hexanes) provided 0.646 g (59%) of ynamide **326** as a yellow oil: IR (neat) 2957, 2231, 2178, 1736, 1614, and 1441 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.19 (s, 1H), 5.13 (s, 1H), 3.77 (s, 3H), 3.60 (t, $J = 7.5$ Hz, 2H), 2.62 (t, $J = 7.5$ Hz, 2H), 1.82 (s, 3H), and 0.15 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 155.4, 126.9, 121.3, 95.0, 84.8, 83.5, 72.6, 54.2, 49.0, 23.7, 18.6, and 0.3; HRMS-ESI m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{14}\text{H}_{21}\text{NO}_2\text{Si}$, 286.1234; found, 286.1245.



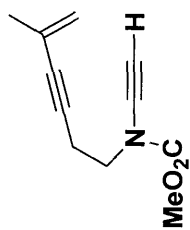
326



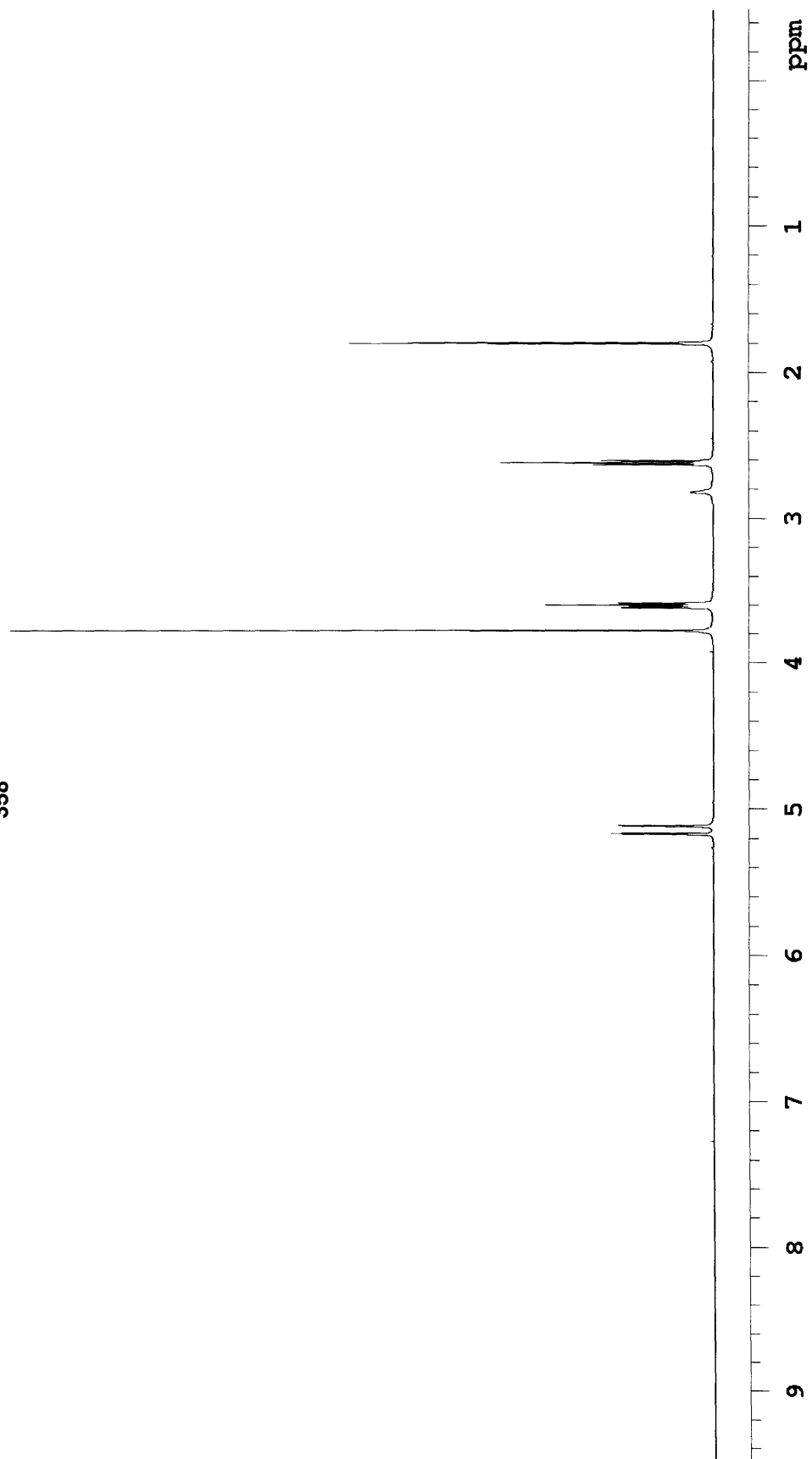


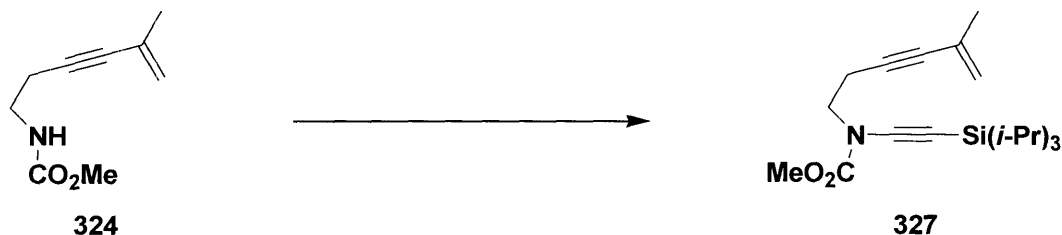
***N*-(Methoxycarbonyl)-*N*-(ethynyl)-5-methyl-5-hexen-3-ynylamine (358).**

A 100-mL round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with ynamide **326** (0.489 g, 1.85 mmol) and 60 mL of THF. The solution was cooled at 0 °C while 2.4 mL of *n*-Bu₄NF solution (1.0 M in THF, 2.4 mmol) was added via syringe, and the resulting dark red solution was stirred at 0 °C for 20 min. The reaction mixture was diluted with 80 mL of Et₂O, washed with 80 mL of satd NaCl solution, dried over MgSO₄, filtered, and concentrated to provide 0.566 g of a dark red oil. Column chromatography on 80 g silica gel (elution with 3% EtOAc-hexanes) provided 0.272 g (77%) of ynamine **358** as a pale yellow oil: IR (neat) 3297, 2956, 2230, 2146, 1733, 1614, and 1442 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.17 (s, 1H), 5.11 (s, 1H), 3.77 (s, 3H), 3.60 (t, *J* = 7.3 Hz, 2H), 2.82 (s, 1H), 2.62 (t, *J* = 7.3 Hz, 2H), and 1.80 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 155.5, 126.8, 121.3, 84.6, 83.6, 76.0, 59.1, 54.2, 48.7, 23.5, and 18.6; HRMS-ESI *m/z*: [M+Na]⁺ calcd for C₁₁H₁₃NO₂, 214.0838; found, 214.0837.



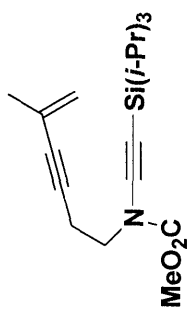
358



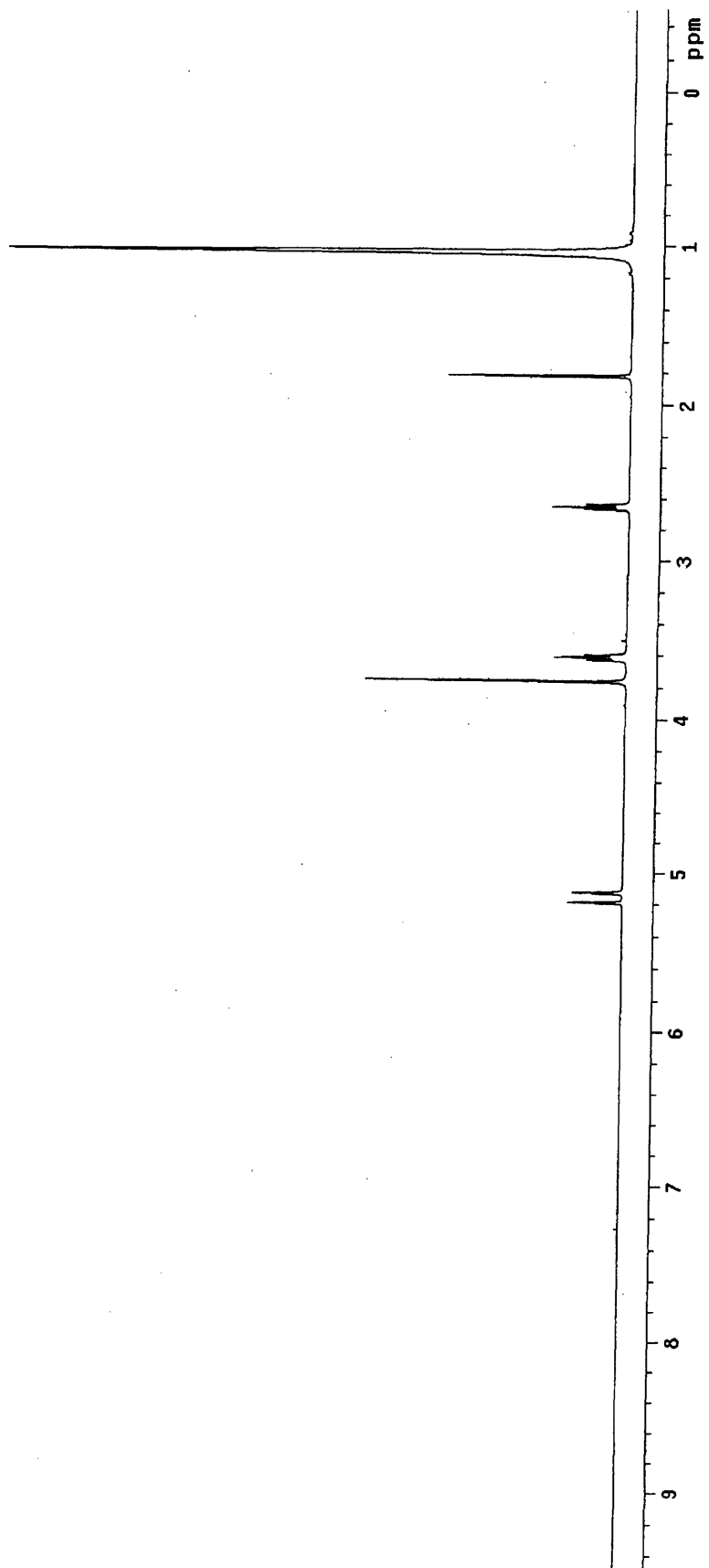


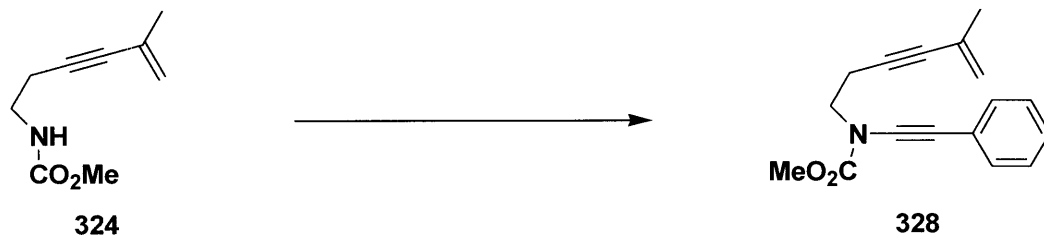
***N*-(Methoxycarbonyl)-*N*-[2-(triisopropylsilyl)ethynyl]-5-methyl-5-hexen-3-ynylamine (327).**

Reaction of a solution of carbamate **324** (0.616 g, 3.68 mmol) in 15 mL of pyridine with KHMDS (4.1 mL, 0.91 M in THF, 3.7 mmol), CuI (0.702 g, 3.69 mmol) in 8 mL of pyridine, and 1-bromo-2-(triisopropylsilyl)acetylene (**228**) (12 mL, 0.60 M in benzene, 7.2 mmol) according to the general procedure gave 1.853 g of a dark red oil. Column chromatography on 80 g of silica gel (gradient elution with 0–5% EtOAc-hexanes) provided 0.815 g (64%) of ynamide **327** as a dark red oil: IR (neat) 2943, 2865, 2227, 2177, 1736, 1614, 1462, 1441, 1372, 1287, 1201, 1128, 995, and 883 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.19 (s, 1H), 5.13 (s, 1H), 3.76 (s, 3H), 3.61 (t, $J = 7.5$ Hz, 2H), 2.65 (t, $J = 7.5$ Hz, 2H), 1.82 (s, 3H), and 1.04 (s, 21H); ^{13}C NMR (125 MHz, CDCl_3) δ 155.8, 126.9, 121.3, 96.3, 84.7, 83.5, 69.1, 54.0, 48.7, 23.7, 18.7, 18.6, and 11.5.



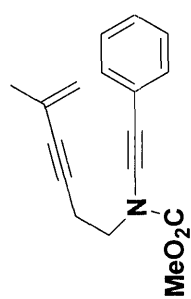
327



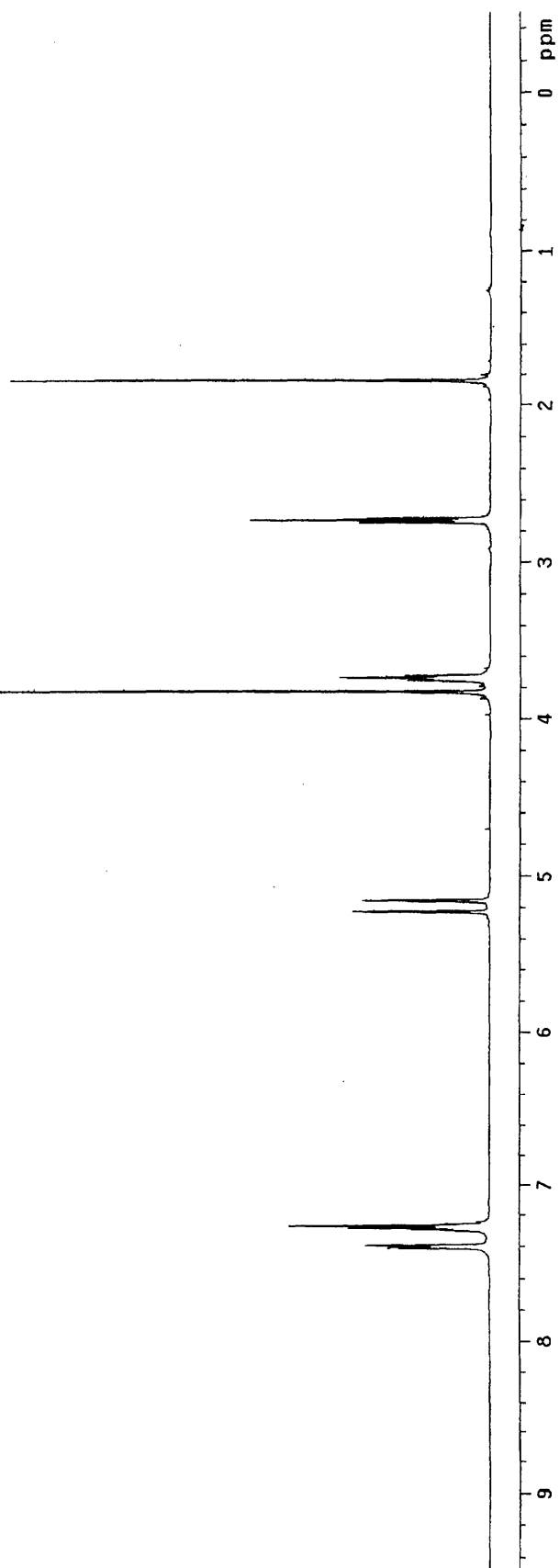


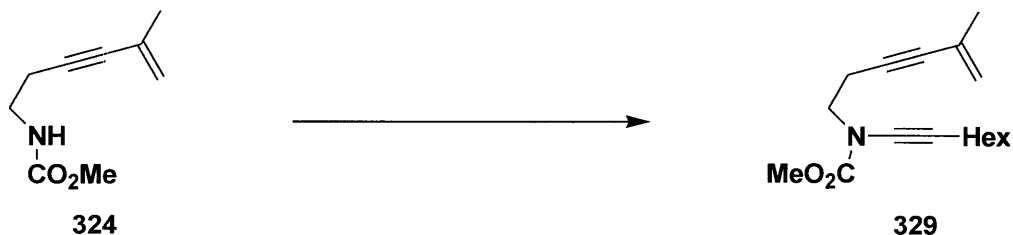
***N*-(Methoxycarbonyl)-*N*-(2-phenylethynyl)-5-methyl-5-hexen-3-ynylamine (**328**).**

Reaction of a solution of carbamate **324** (0.338 g, 2.02 mmol) in 8.0 mL of pyridine with KHMDS (2.2 mL, 0.91 M in THF, 2.0 mmol), CuI (0.386 g, 2.03 mmol) in 4.0 mL of pyridine, and 1-bromo-2-phenylacetylene (**224**) (6.7 mL, 0.60 M in benzene, 4.0 mmol) according to the general procedure gave 0.794 g of a dark red oil. Column chromatography on 50 g of silica gel (gradient elution with 0–5% EtOAc-hexanes) provided 0.329 g (62%) of ynamide **328** as an orange oil: IR (neat) 2955, 2336, 2252, 1733, 1614, 1599, 1441, 1394, 1308, 1248, 1223, 1152, 1118, 1025, 898, 757, and 692 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.39–7.41 (m, 2H), 7.26–7.30 (m, 3H), 5.23 (s, 1H), 5.16 (s, 1H), 3.83 (s, 3H), 3.74 (t, $J = 7.3$ Hz, 2H), 2.73 (t, $J = 7.3$ Hz, 2H), and 1.84 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 155.4, 131.3, 128.3, 127.8, 126.9, 123.1, 121.4, 83.6, 82.4, 70.8, 54.2, 49.2, 23.7, and 18.9; HRMS-ESI m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{17}\text{NO}_2$, 290.1151; found, 290.1150.



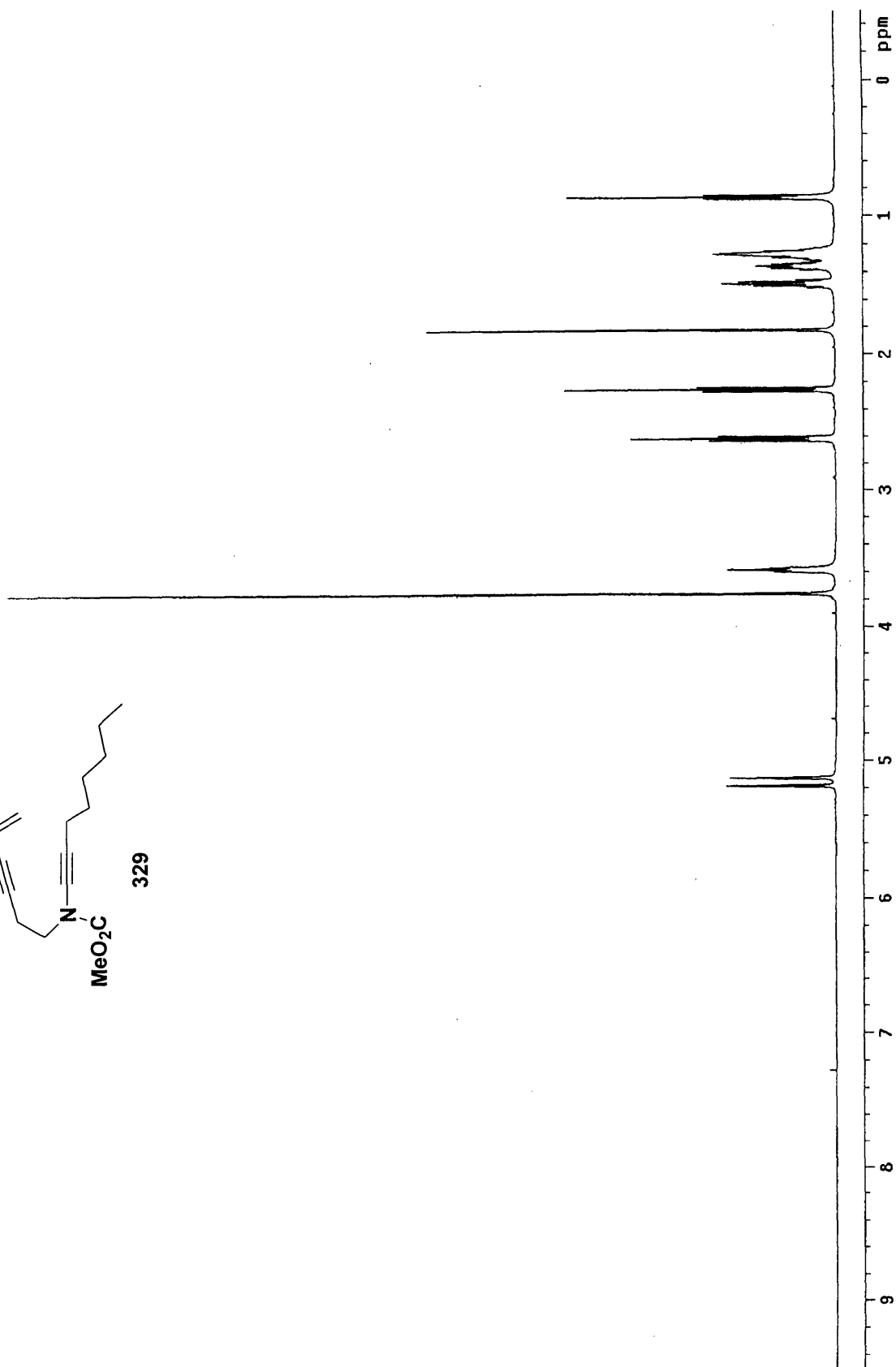
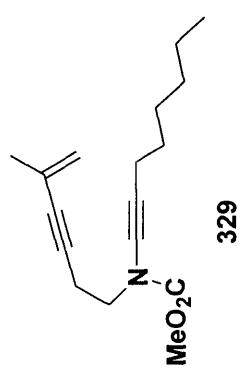
328

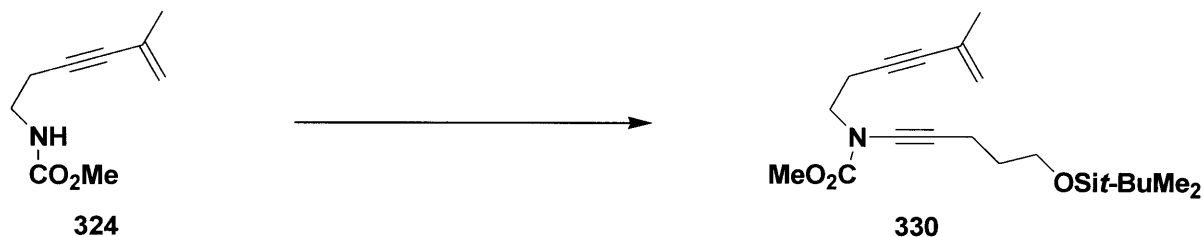




***N*-(Methoxycarbonyl)-*N*-(5-methyl-5-hexen-3-ynyl)-1-octynylamine (**329**).**

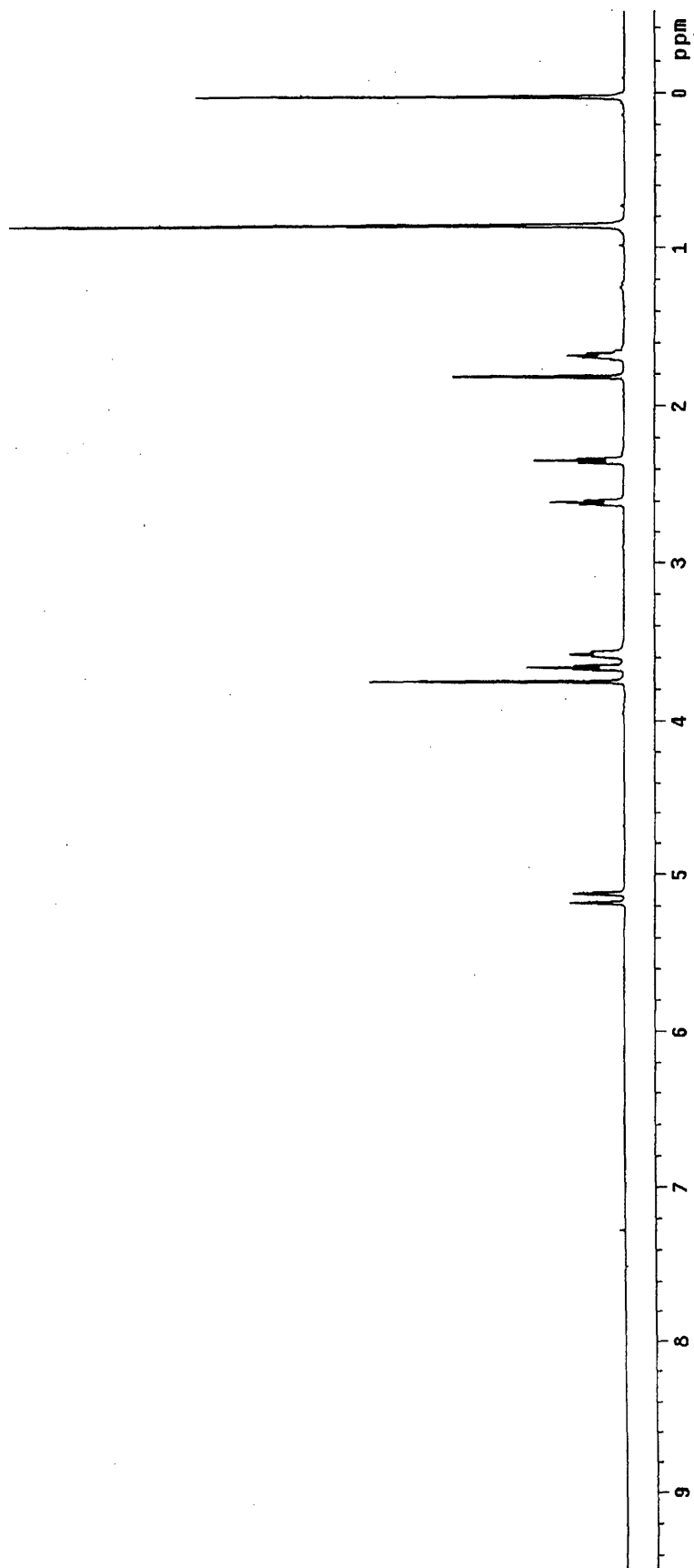
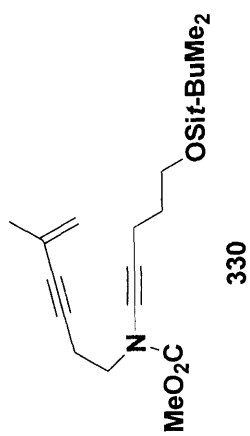
Reaction of a solution of carbamate **324** (0.208 g, 1.24 mmol) in 5.0 mL of pyridine with KHMDS (1.4 mL, 0.91 M in THF, 1.3 mmol), CuI (0.243 g, 1.28 mmol) in 2.5 mL of pyridine, and 1-bromo-1-octyne (**227**) (4.1 mL, 0.60 M in benzene, 2.5 mmol) according to the general procedure gave 0.570 g of a dark red oil. Column chromatography on 25 g of silica gel (gradient elution with 0–5% EtOAc-hexanes) provided 0.173 g (51%) of ynamide **329** as an orange oil: IR (neat) 3096, 2955, 2931, 2858, 2263, 1729, 1613, 1443, 1390, 1292, 1204, 1135, 895, 763, and 734 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.18 (s, 1H), 5.13 (s, 1H), 3.76 (s, 3H), 3.58 (t, $J = 7.5$ Hz, 2H), 2.61 (t, $J = 7.5$ Hz, 2H), 2.25 (t, $J = 7.1$ Hz, 2H), 1.82 (s, 3H), 1.48 (app quint, $J = 7.2$ Hz, 2H), 1.33–1.39 (m, 2H), 1.24–1.31 (m, 4H), and 0.86 (t, 6.9 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 156.0, 126.7, 121.2, 85.0, 83.4, 73.2, 70.3, 54.0, 49.0, 39.6, 31.4, 29.1, 28.6, 23.7, 22.7, 18.6, and 14.1; HRMS-ESI m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{25}\text{NO}_2$, 298.1778; found, 298.1772.

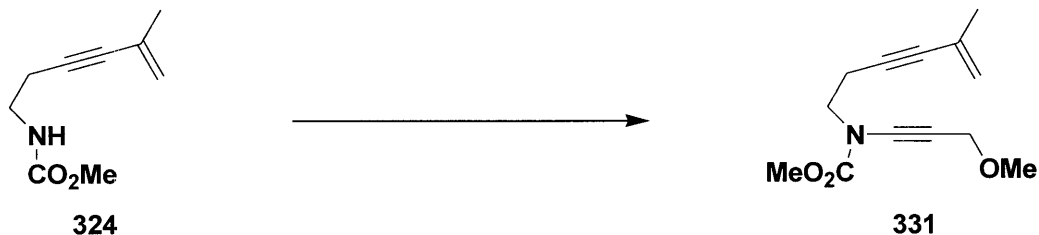




***N*-(Methoxycarbonyl)-*N*-[5-(*tert*-butyldimethylsiloxy)-1-pentynyl]-5-methyl-5-hexen-3-ynylamine (**330**).**

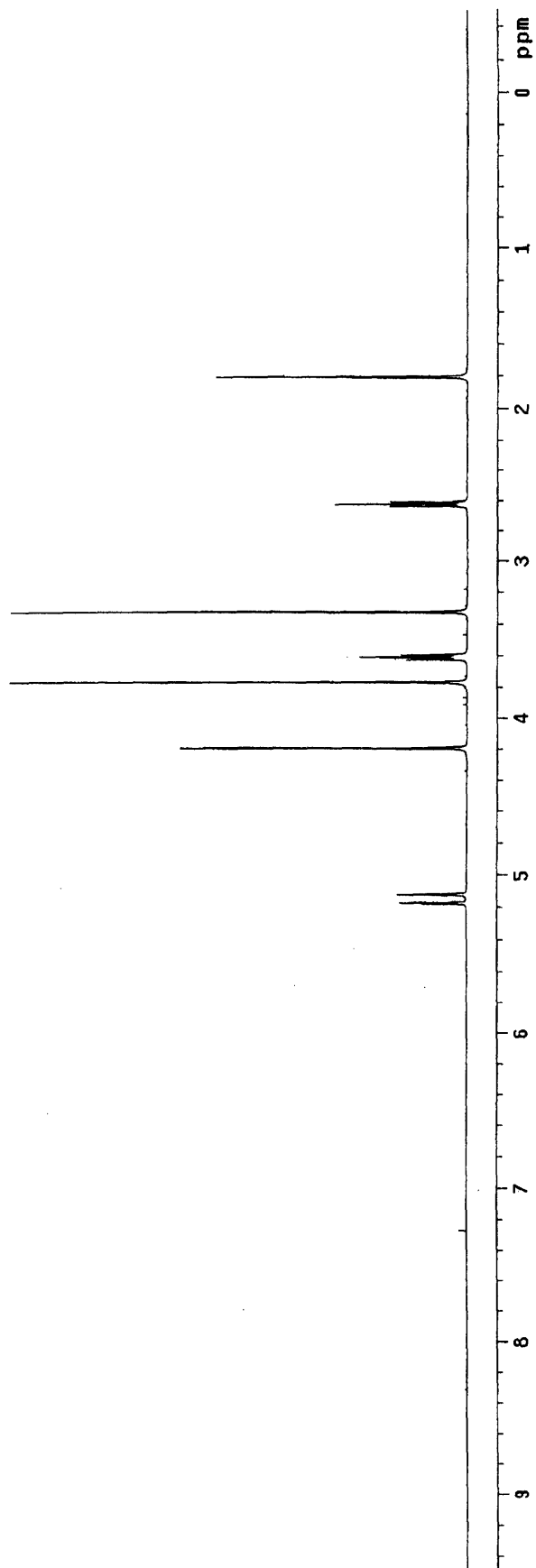
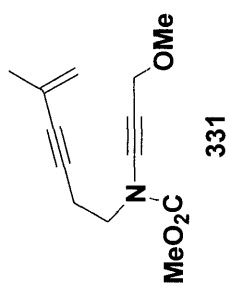
Reaction of a solution of carbamate **324** (0.198 g, 1.18 mmol) in 4.8 mL of pyridine with KHMDS (1.3 mL, 0.91 M in THF, 1.2 mmol), CuI (0.225 g, 1.18 mmol) in 2.4 mL of pyridine, and 1-bromo-5-(*tert*-butyldimethylsiloxy)-1-pentyne (**229**) (4.0 mL, 0.60 M in benzene, 2.4 mmol) according to the general procedure gave 0.675 g of a dark brown oil. Column chromatography on 25 g of silica gel (gradient elution with 0.5–3% EtOAc-hexanes) provided 0.170 g (40%) of ynamide **330** as a yellow oil: IR (neat) 2954, 2857, 2265, 2231, 1730, 1612, 1443, 1390, 1291, 1252, 1204, 1105, 836, and 777 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.18 (s, 1H), 5.12 (s, 1H), 3.75 (s, 3H), 3.66 (t, *J* = 7.3 Hz, 2H), 3.57 (t, *J* = 7.0 Hz, 2H), 2.60 (t, *J* = 7.3 Hz, 2H), 2.34 (t, *J* = 7.0 Hz, 2H), 1.81 (s, 3H), 1.68 (m, 2H), 0.86 (s, 9H), and 0.02 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 156.0, 126.9, 121.2, 85.0, 83.4, 73.3, 69.8, 61.7, 54.0, 49.0, 32.1, 26.0, 23.7, 18.6, 18.4, 15.0, and -5.3; HRMS-ESI *m/z*: [M+Na]⁺ calcd for C₂₀H₃₃NO₃Si, 386.2122; found, 386.2105.

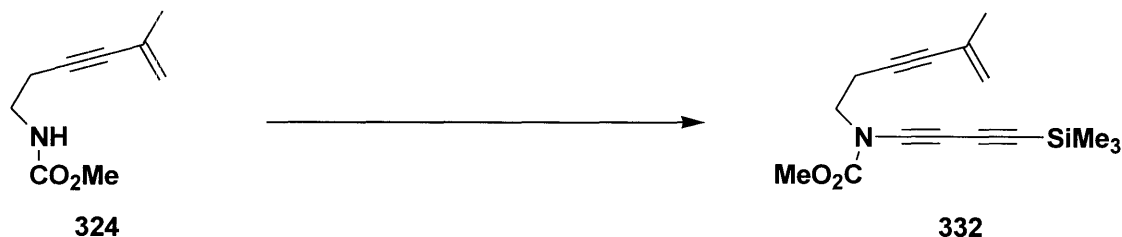




***N*-(Methoxycarbonyl)-*N*-(3-methoxy-1-propynyl)-5-methyl-5-hexen-3-ynylamine (**331**).**

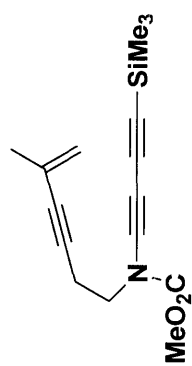
Reaction of a solution of carbamate **324** (0.452 g, 2.70 mmol) in 11 mL of pyridine with KHMDS (3.0 mL, 0.91 M in THF, 2.7 mmol), CuI (0.516 g, 2.71 mmol) in 5 mL of pyridine, and 1-bromo-3-methoxy-1-propyne (**225**) (6.9 mL, 0.60 M in benzene, 5.4 mmol) according to the general procedure gave 0.812 g of a dark red oil. Column chromatography on 80 g of silica gel (elution with 5% EtOAc-hexanes) provided 0.245 g (39%) of ynamide **331** as a yellow oil: IR (neat) 2955, 2251, 1732, 1614, 1444, 1392, 1355, 1294, 1297, 1208, 1134, 1098, 997, 900, and 763 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.17 (s, 1H), 5.12 (s, 1H), 4.19 (s, 2H), 3.76 (s, 3H), 3.61 (t, $J = 7.3$ Hz, 2H), 3.32 (s, 3H), 2.62 (t, $J = 7.3$ Hz, 2H), and 1.81 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 155.6, 126.9, 121.3, 84.7, 83.5, 79.6, 66.9, 60.1, 57.3, 54.2, 48.9, 23.6, and 18.7; GC-MS m/z : 235 (M^+).



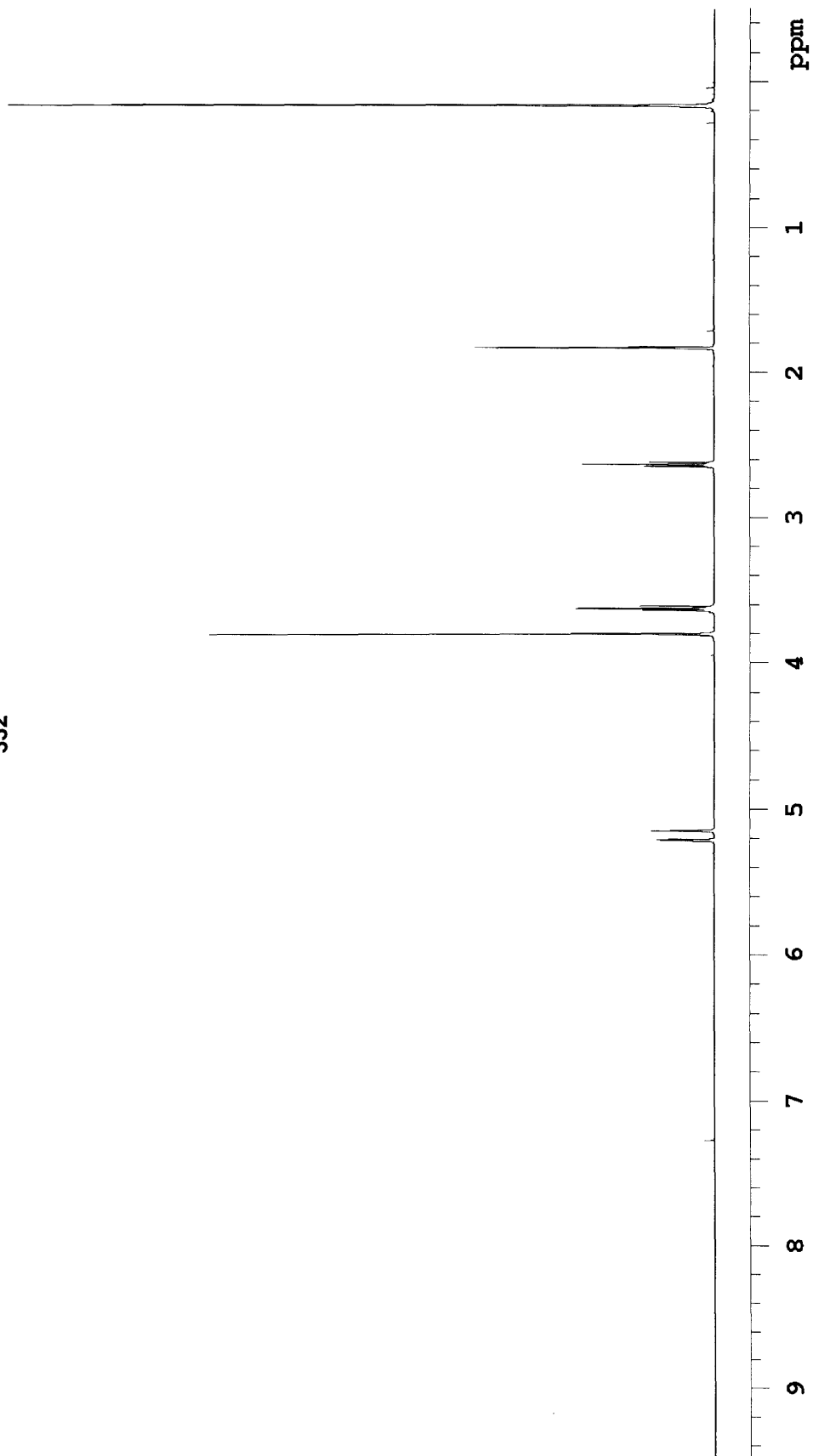


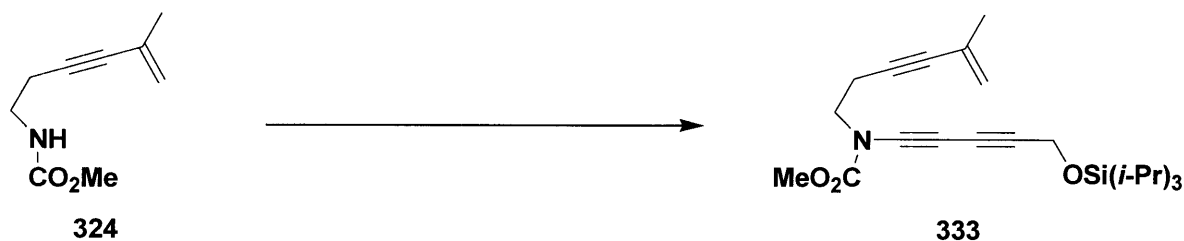
***N*-(Methoxycarbonyl)-*N*-[4-(trimethylsilyl)-1,3-butadiynyl]-5-methyl-5-hexen-3-ynylamine (332).**

Reaction of a solution of carbamate **324** (0.287 g, 1.72 mmol) in 7.0 mL of pyridine with KHMDS (1.9 mL, 0.91 M in THF, 1.7 mmol), CuI (0.330 g, 1.73 mmol) in 3.6 mL of pyridine, and 1-bromo-4-(trimethylsilyl)-1,3-butadiyne (**242**) (8.5 mL, 0.40 M in benzene, 3.4 mmol) according to the general procedure gave 0.659 g of a dark brown oil. Column chromatography on 50 g of silica gel (elution with benzene) provided 0.147 g (30%) of ynamide **332** as a yellow oil: IR (neat) 2957, 2233, 2113, 1743, 1613, and 1440 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.21 (s, 1H), 5.15 (s, 1H), 3.80 (s, 3H), 3.63 (t, $J = 7.2$ Hz, 2H), 2.63 (t, $J = 7.2$ Hz, 2H), 1.83 (s, 3H), and 0.17 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 155.4, 126.8, 121.5, 90.0, 87.5, 84.3, 83.9, 69.2, 58.5, 54.5, 49.0, 23.6, 18.9, and -0.3 ; HRMS-ESI m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_2\text{Si}$, 310.1234; found, 310.1231.



332

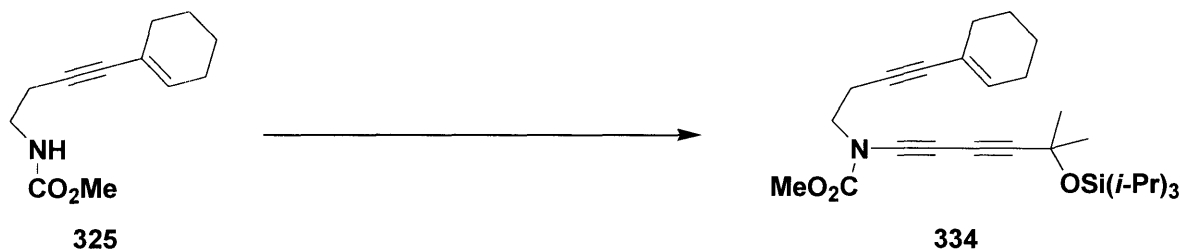




***N*-(Methoxycarbonyl)-*N*-[5-(triisopropylsiloxy)-1,3-pentadiynyl]-5-methyl-5-hexen-3-ynylamine (**333**).**

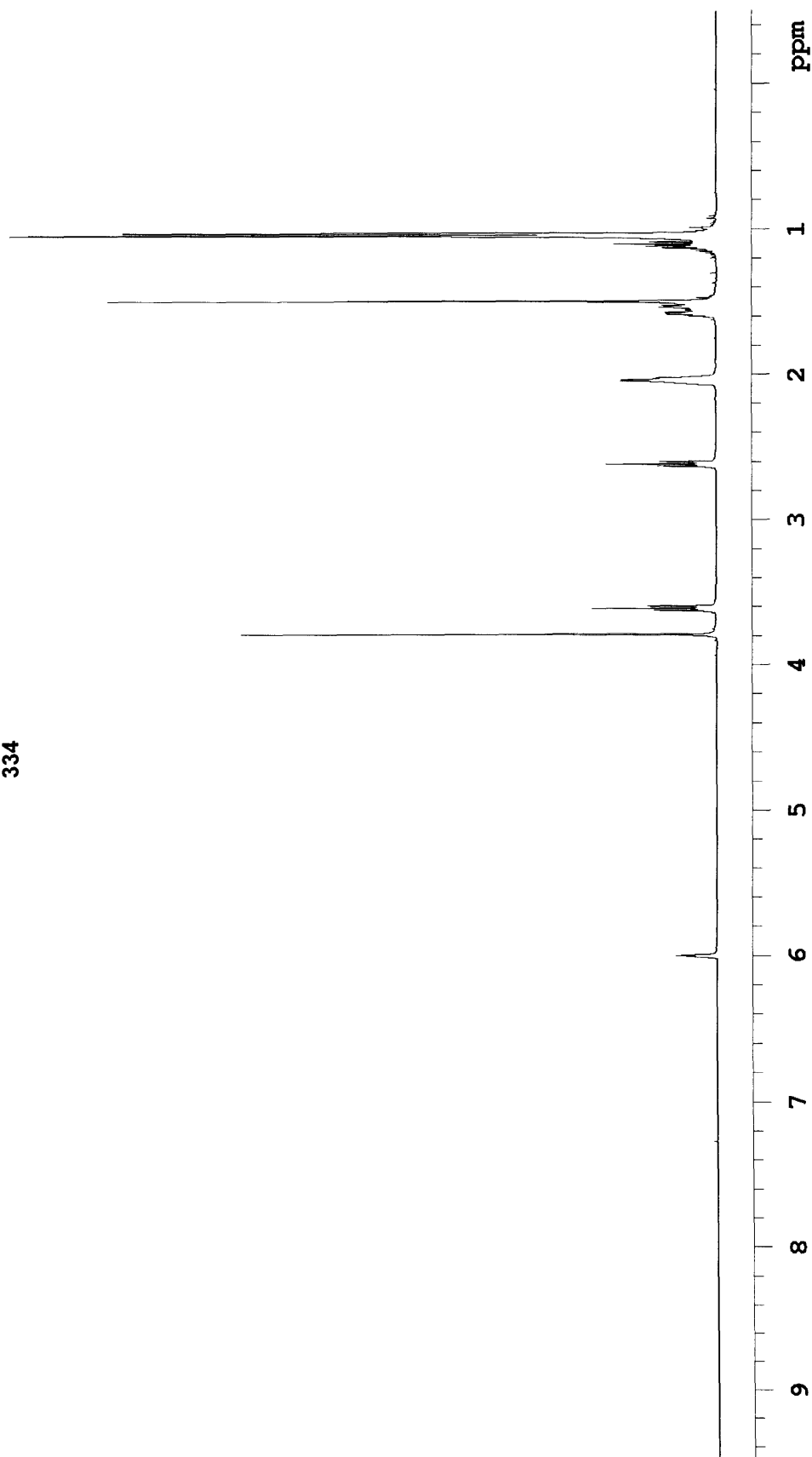
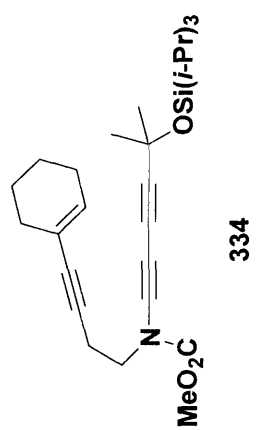
Reaction of a solution of carbamate **324** (0.414 g, 2.48 mmol) in 10 mL of pyridine with KHMDS (2.8 mL, 0.90 M in THF, 2.5 mmol), CuI (0.480 g, 2.52 mmol) in 5 mL of pyridine, and 1-bromo-5-(triisopropylsiloxy)-1,3-pentadiyne (**249**) (6.1 mL, 0.60 M in benzene, 3.7 mmol) according to the general procedure gave 1.499 g of a dark brown oil. Column chromatography on 100 g of silica gel (gradient elution with 0–5% EtOAc-hexanes) provided 0.494 g (50%) of ynamide **333** as a red oil: IR (neat) 2945, 2866, 2259, 2172, 1741, 1613, and 1441 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.24 (s, 1H), 5.18 (s, 1H), 4.49 (s, 2H), 3.83 (s, 3H), 3.66 (t, J = 7.2 Hz, 2H), 2.67 (t, J = 7.2 Hz, 2H), 1.86 (s, 3H), 1.13 (sept, J = 5.5 Hz, 3H), and 1.08 (d, J = 5.5 Hz, 18H); ^{13}C NMR (125 MHz, CDCl_3) δ 155.5, 126.8, 121.4, 84.4, 83.9, 81.3, 70.5, 68.8, 57.7, 54.5, 52.6, 49.1, 23.6, 18.9, 18.0, and 12.1; HRMS-ESI m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{23}\text{H}_{35}\text{NO}_3\text{Si}$, 424.2278; found, 424.2269.

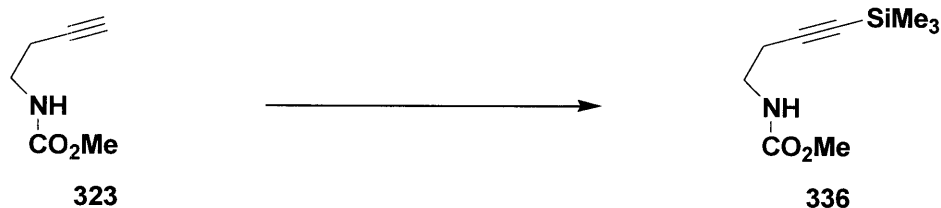




***N*-(Methoxycarbonyl)-*N*-[4-(1-Cyclohexenyl)-3-butynyl]-5-(triisopropylsiloxy)-5-methyl-1,3-hexadienylamine (**334**).**

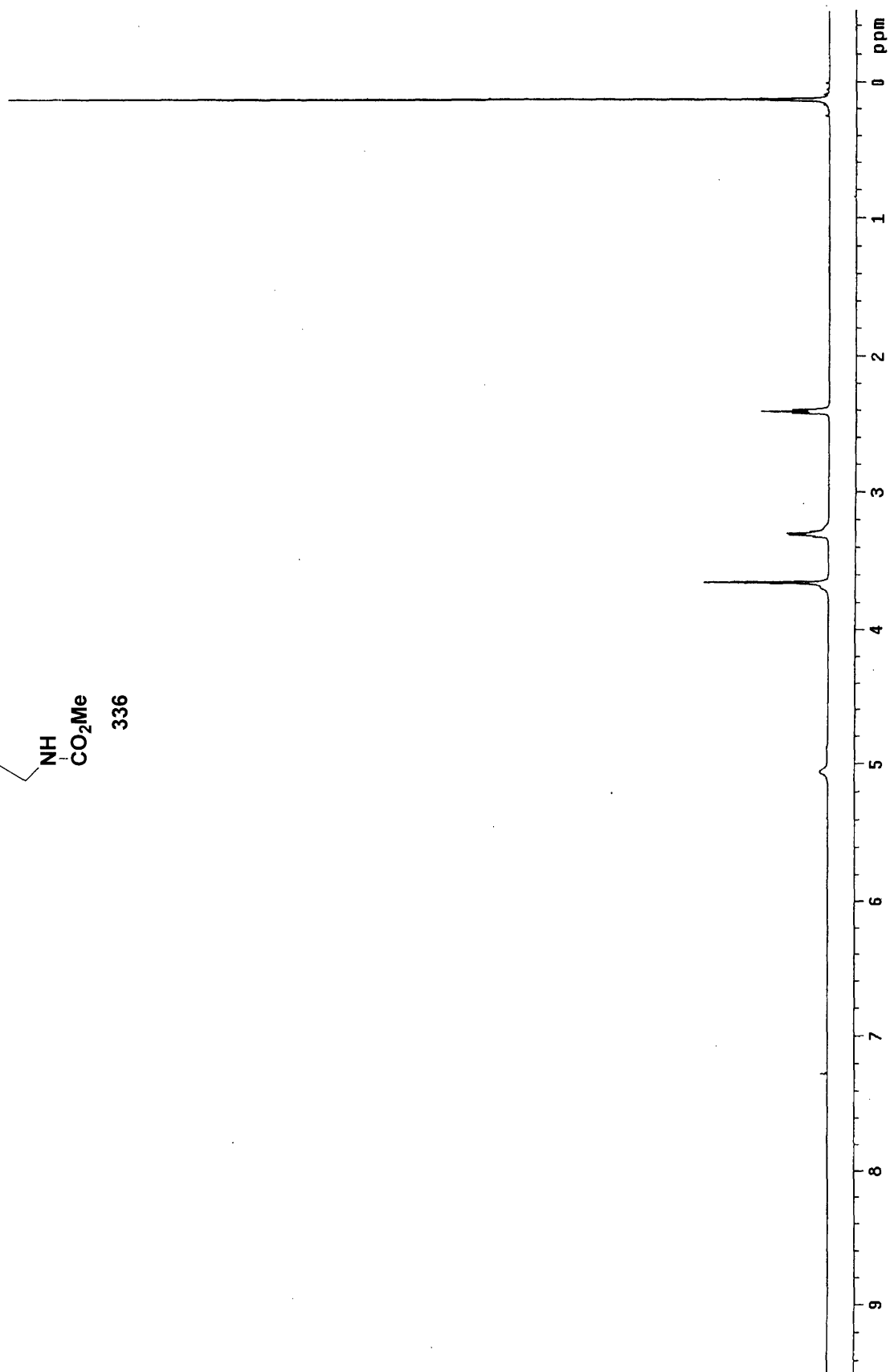
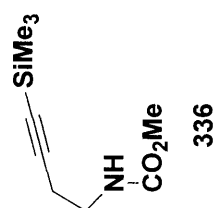
Reaction of a solution of carbamate **325** (0.212 g, 1.02 mmol) in 4.0 mL of pyridine with KHMDS (1.13 mL, 0.90 M in THF, 1.0 mmol), CuI (0.195 g, 1.03 mmol) in 2.0 mL of pyridine, and 1-bromo-5-(triisopropylsiloxy)-5-methyl-1,3-hexadiyne (**254**) (2.6 mL, 0.58 M in benzene, 1.5 mmol) according to the general procedure gave 0.596 g of a dark brown oil. Column chromatography on 40 g of silica gel (gradient elution with 0–15% EtOAc-hexanes) provided 0.244 g (51%) of ynamide **334** as a pale brown oil: IR (neat) 2942, 2865, 2253, 2167, 1738, and 1440 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.00 (m, 1H), 3.79 (s, 3H), 3.61 (t, $J = 7.3$ Hz, 2H), 2.62 (t, $J = 7.3$ Hz, 2H), 2.01–2.06 (m, 4H), 1.52–1.60 (m, 4H), 1.50 (s, 6H), 1.11 (sept, $J = 6.7$ Hz, 3H), and 1.04 (d, $J = 6.7$ Hz, 18H); ^{13}C NMR (125 MHz, CDCl_3) δ 155.5, 134.3, 120.7, 87.6, 84.4, 82.4, 70.9, 67.0, 66.8, 57.4, 54.5, 49.3, 33.1, 29.4, 25.7, 22.5, 21.7, 18.9, 18.4, and 13.1; HRMS-ESI m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{28}\text{H}_{43}\text{NO}_3\text{Si}$, 492.2904; found, 492.2906.

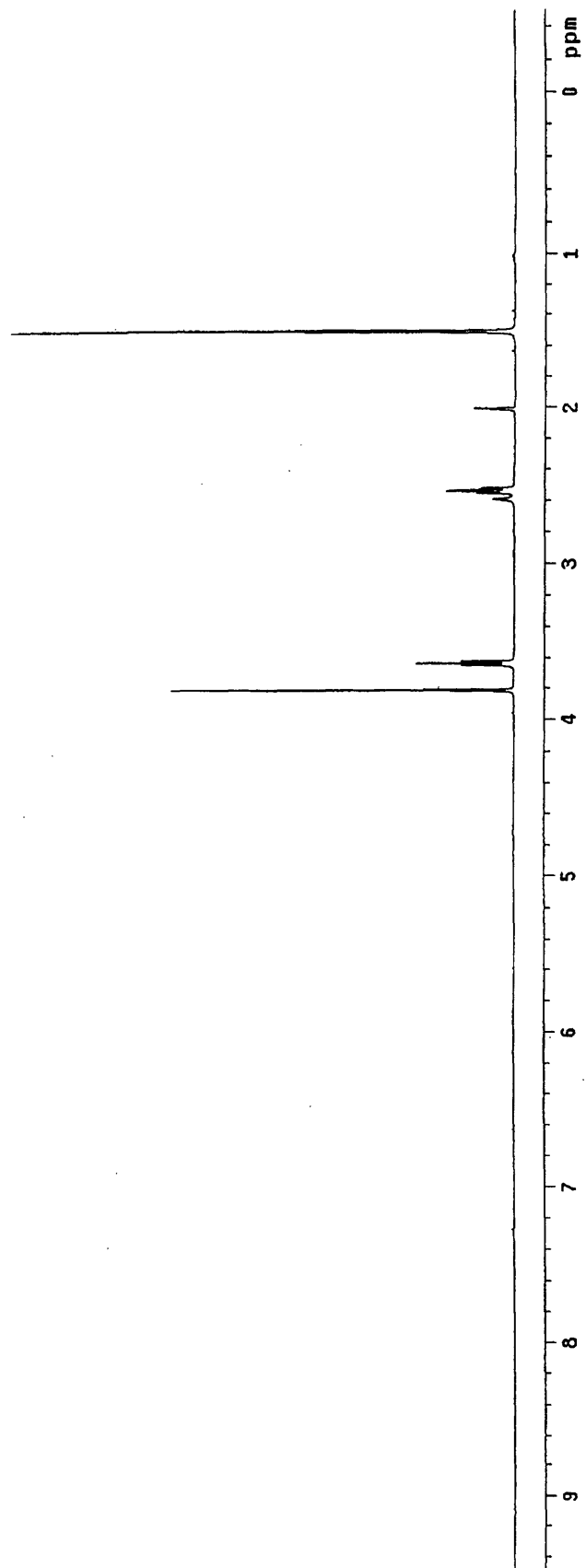
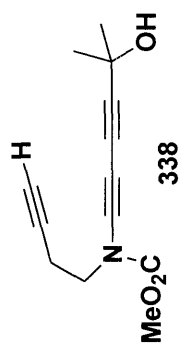




***N*-(Methoxycarbonyl)-4-(trimethylsilyl)-3-butanamine (336).**

A 250-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with alkyne **323** (3.346 g, 26.32 mmol) and 130 mL of THF and cooled at $-78\text{ }^{\circ}\text{C}$ while 22.4 mL of *n*-BuLi solution (2.35 M in hexanes, 52.6 mmol) was added via syringe over 5 min. The resulting viscous, white mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 15 min. Chlorotrimethylsilane (6.7 mL, 5.7 g, 53 mmol) was then added via syringe over 2 min, the ice bath was removed, and the resulting solution was stirred at rt for 90 min. 2 M HCl (60 mL) was next added, and the biphasic solution was stirred at rt for 1 h. The volatile organic solvents (THF and hexanes) were removed by rotary evaporation at rt and 20 mmHg, and the resulting aqueous solution was extracted with three 100-mL portions of Et₂O. The combined organic layers were washed with 150 mL of satd NaCl solution, dried over MgSO₄, filtered, and concentrated to give 5.376 g of a yellow oil. Column chromatography on 120 g silica gel (gradient elution with 10–20% EtOAc-hexanes) provided 4.420 g (84%) of silyl alkyne **336** as a colorless oil: IR (neat) 3338, 2958, 2177, 1708, 1535, and 1449 cm^{-1} ; ¹H NMR (500 MHz, CDCl₃) δ 4.90 and 5.06 (NH rotamers, br s, 1H), 3.65 (s, 3H), 3.30 (dt, $J = 6.1, 6.4$ Hz, 2H), 2.41 (t, $J = 6.4$ Hz, 2H), and 0.13 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 156.9, 103.9, 86.1, 51.9, 39.7, 21.1, and -0.1 ; HRMS-ESI m/z : $[\text{M}+\text{Na}]^{+}$ calcd for C₉H₁₇NO₂Si, 222.0921; found, 222.0920.

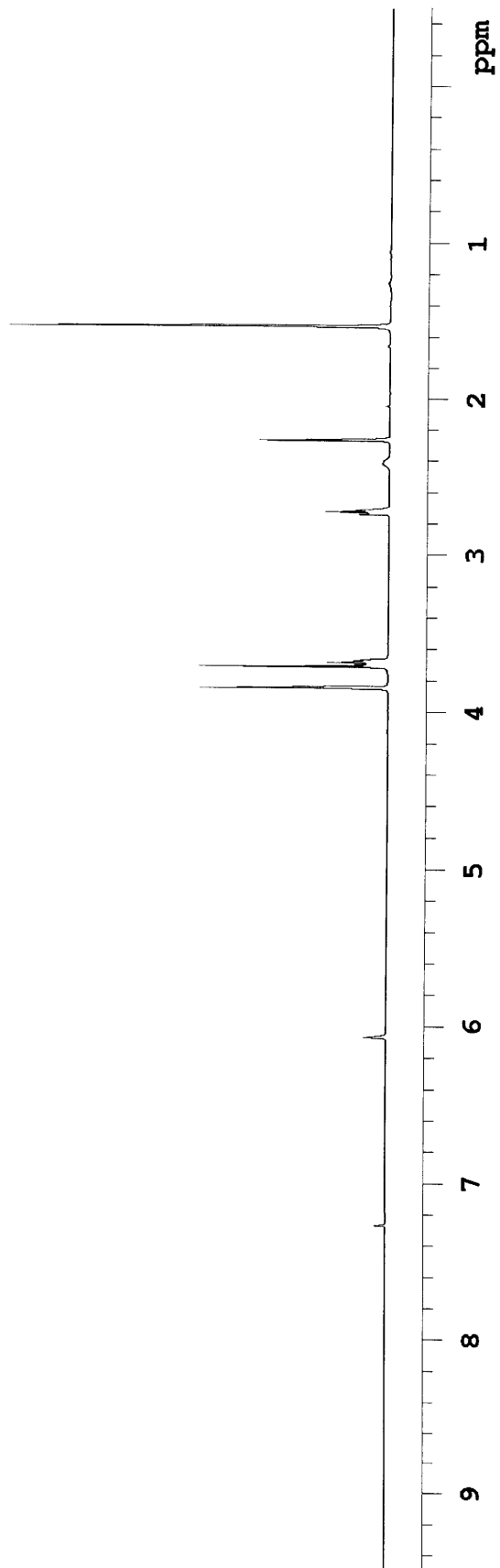


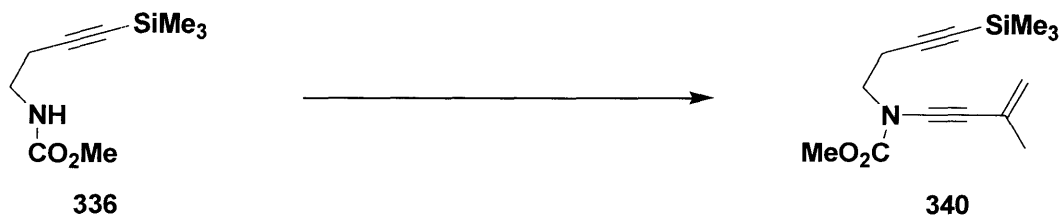




***N*-(Methoxycarbonyl)-*N*-(6-methoxycarbonyl-5-methyl-5-hexen-3-ynyl)-5-hydroxy-5-methyl-1,3-hexadiynylamine (**335**).**

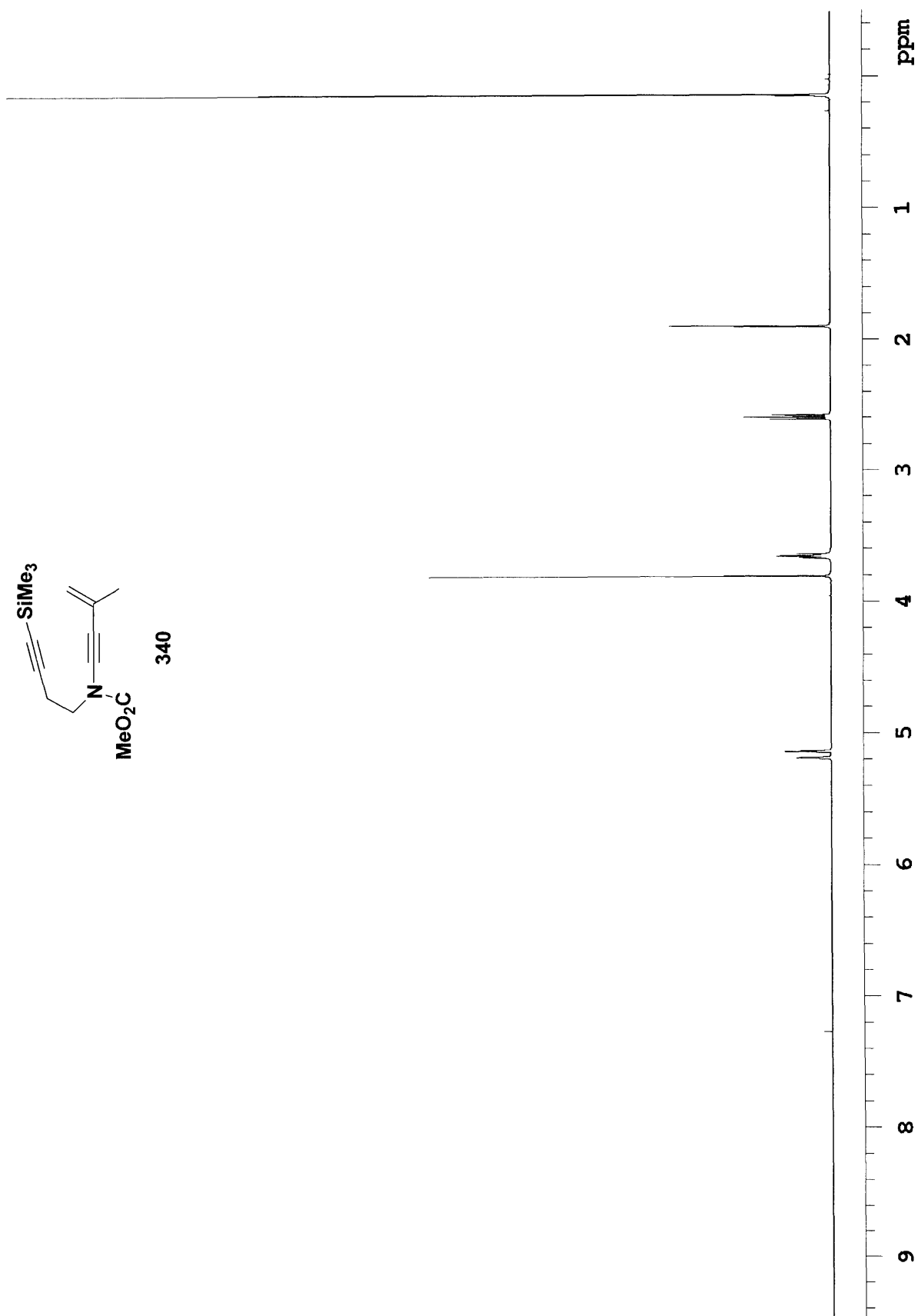
A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ (0.041 g, 0.058 mmol) and CuI (0.023 g, 0.12 mmol) and cooled at 0 °C while a solution of alkyne **338** (0.459 g, 1.97 mmol) in 2.0 mL of Et_3N was added via cannula in one portion (two 0.5-mL Et_3N rinses). A solution of methyl (*E*)-3-iodo-2-butenate (**339**) (3.0 mL, 1.0 M in THF, 3.0 mmol) was added, the ice bath was removed, and the resulting dark red suspension was stirred at room temperature for 1 h. The reaction mixture was diluted with 50 mL of Et_2O and filtered through a 5 x 2.5 cm plug of silica gel with the aid of 300 mL of Et_2O . Concentration of the filtrate afforded 0.720 g of a dark red oil. Column chromatography on 40 g of silica gel (elution with 20% EtOAc-hexanes) provided 0.399 g (61%) of enyne **335** as a beige solid: mp 73–74 °C; IR (film) 3471, 2982, 2955, 2255, 2168, 1738, 1721, 1618, and 1440 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.07 (s, 1H), 3.85 (s, 3H), 3.71 (s, 3H), 3.68 (t, J = 6.6 Hz, 2H), 2.72 (t, J = 6.6 Hz, 2H), 2.41 (br s, 1H), 2.27 (s, 3H), and 1.53 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 166.6, 155.4, 138.3, 123.5, 90.8, 87.1, 84.7, 70.7, 66.0, 65.3, 57.3, 54.5, 51.2, 48.6, 31.0, 19.9, and 19.1; HRMS-ESI m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{18}\text{H}_{21}\text{NO}_5$, 354.1312; found, 354.1316.

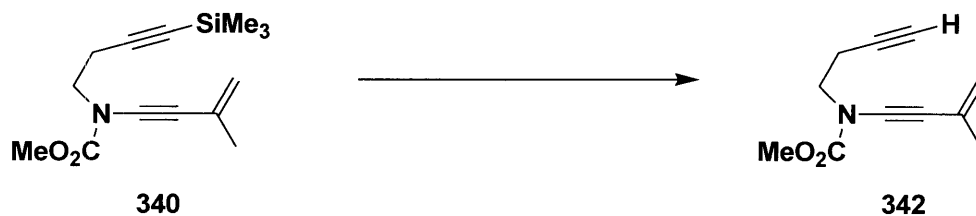




***N*-(Methoxycarbonyl)-*N*-(3-methyl-3-buten-1-ynyl)-4-(trimethylsilyl)-3-butenylamine (**340**).**

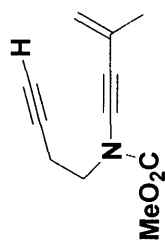
Reaction of a solution of carbamate **336** (0.959 g, 4.81 mmol) in 19 mL of pyridine with KHMDS (5.3 mL, 0.91 M in THF, 4.8 mmol), CuI (0.918 g, 4.82 mmol) in 10 mL of pyridine, and 1-bromo-3-methyl-3-buten-1-yne (**231**) (17 mL, 0.58 M in benzene, 9.6 mmol) according to the general procedure gave 1.425 g of a dark red oil. Column chromatography on 120 g of silica gel (gradient elution with 0–2% EtOAc-hexanes) provided 0.579 g (46%) of ynamide **340** as a yellow oil: IR (neat) 2957, 2236, 2179, 1736, 1613, and 1443 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.19 (s, 1H), 5.14 (s, 1H), 3.81 (s, 3H), 3.65 (t, $J = 7.5$ Hz, 2H), 2.59 (t, $J = 7.5$ Hz, 2H), 1.90 (s, 3H), and 0.14 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 155.4, 126.3, 119.7, 102.6, 86.8, 81.7, 72.2, 54.2, 49.0, 23.8, 19.3, and 0.1; HRMS-ESI m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{14}\text{H}_{21}\text{NO}_2\text{Si}$, 286.1234; found, 286.1239.



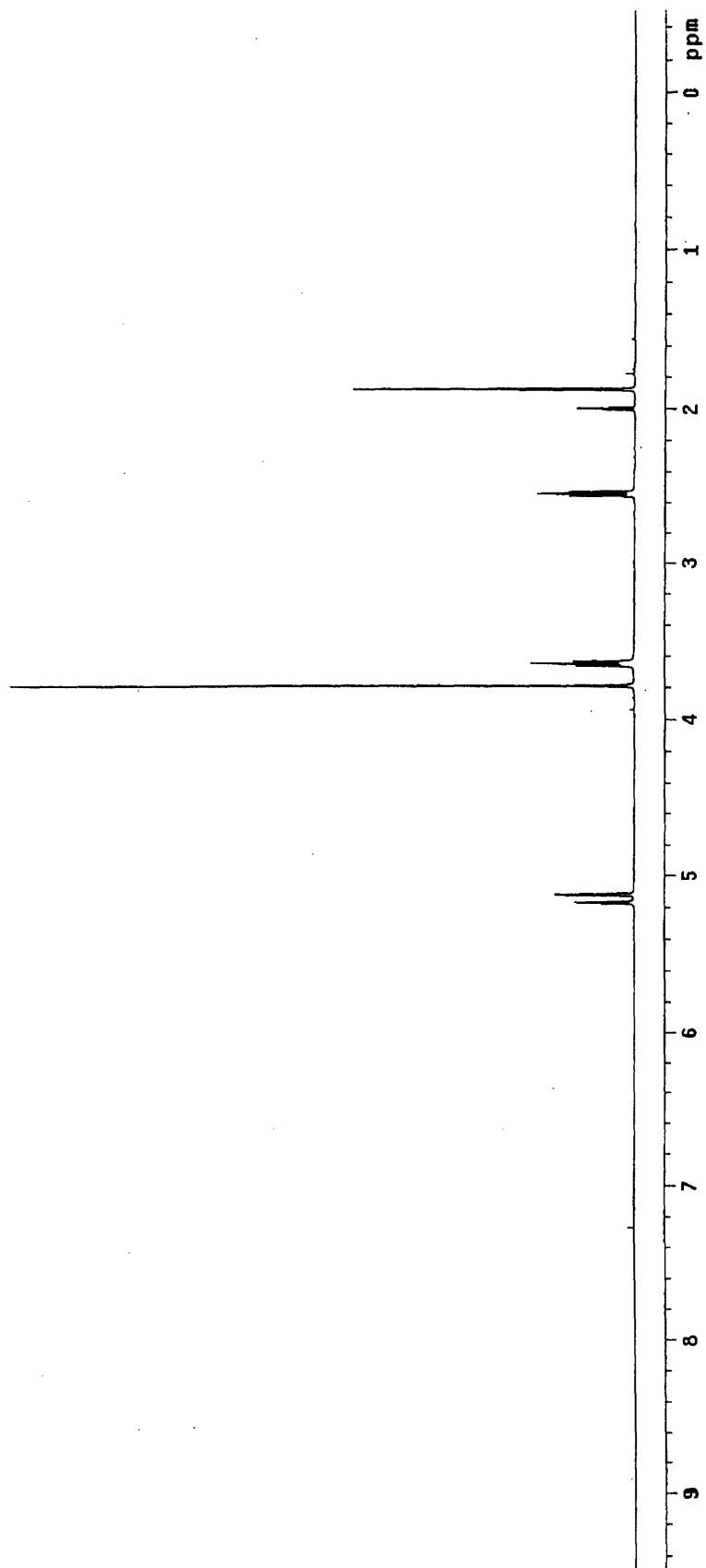


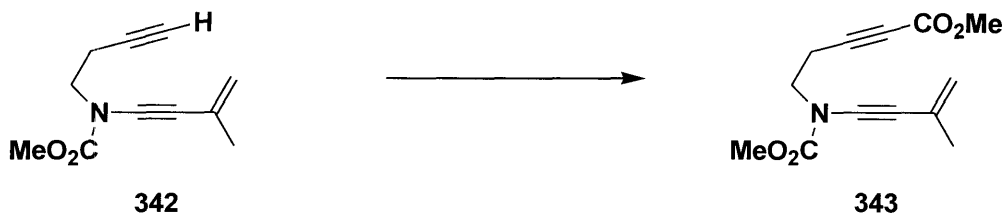
***N*-(Methoxycarbonyl)-*N*-(3-methyl-3-buten-1-ynyl)-3-butynylamine (342).**

A 50-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with silyl alkyne **340** (0.256 g, 0.972 mmol) and 20 mL of THF and cooled at 0 °C while 1.1 mL of *n*-Bu₄NF solution (1.0 M in THF, 1.1 mmol) was added via syringe. The resulting yellow solution was stirred at 0 °C for 15 min and then diluted with 20 mL of Et₂O and extracted with 20 mL of water. The aqueous layer was extracted with two 10-mL portions of Et₂O, and the combined organic layers were washed with 25 mL of satd NaCl solution, dried over MgSO₄, filtered, and concentrated to provide 0.188 g of a dark red oil. Column chromatography on 30 g silica gel (elution with 5% EtOAc-hexanes) provided 0.154 g (83%) of desilylated alkyne **342** as a pale yellow oil: IR (neat) 3293, 2956, 2236, 2122, 1731, 1613, and 1443 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.17 (s, 1H), 5.12 (s, 1H), 3.79 (s, 3H), 3.65 (t, *J* = 7.3 Hz, 2H), 2.54 (dt, *J* = 2.6, 7.3 Hz, 2H), 2.00 (t, *J* = 2.6 Hz, 1H), and 1.88 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 155.4, 126.3, 119.9, 81.5, 80.3, 72.3, 70.3, 54.3, 48.8, 23.7, and 17.9; GC-MS *m/z*: 191 (M⁺).



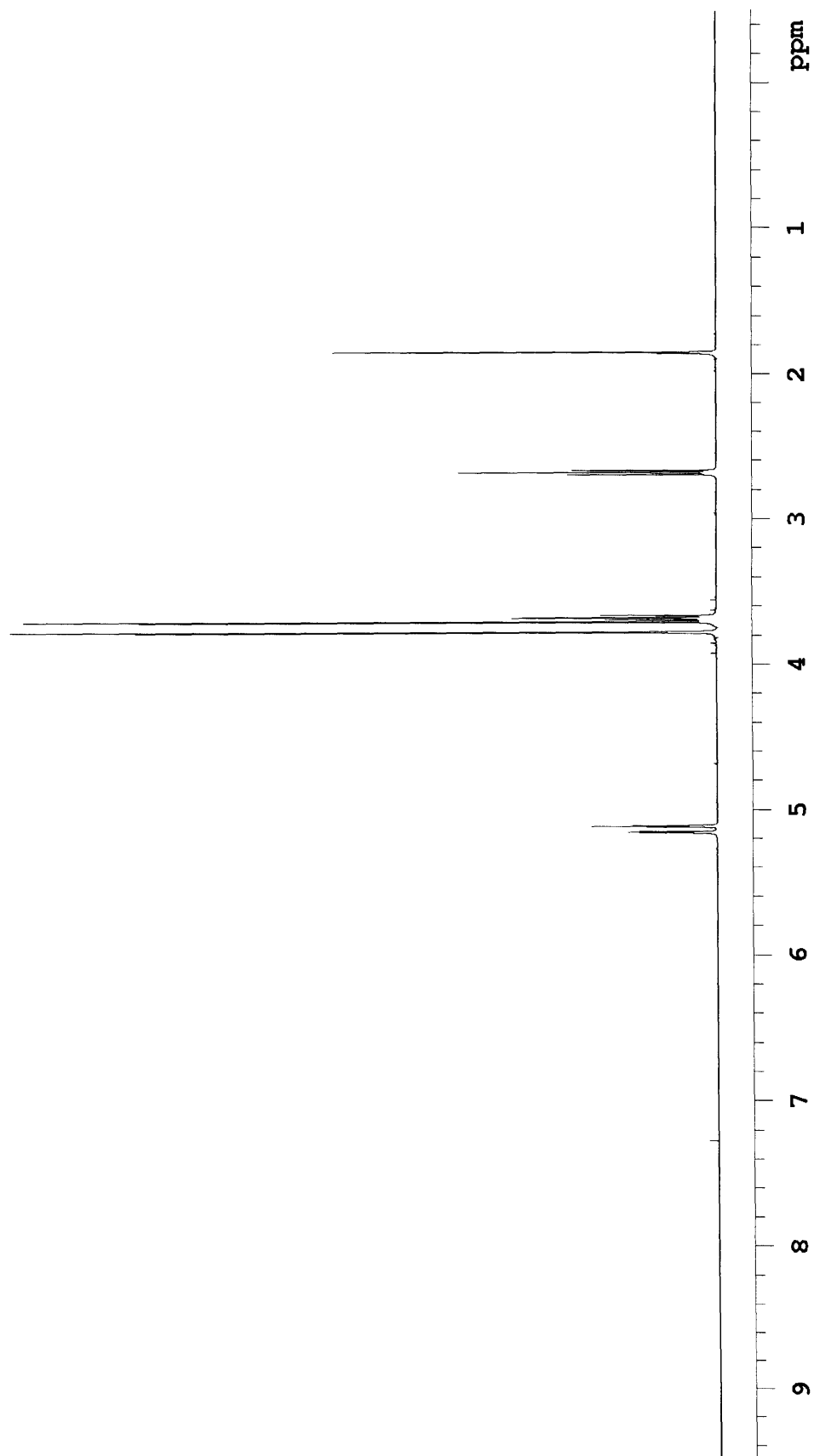
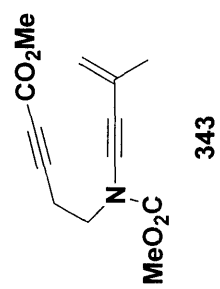
342

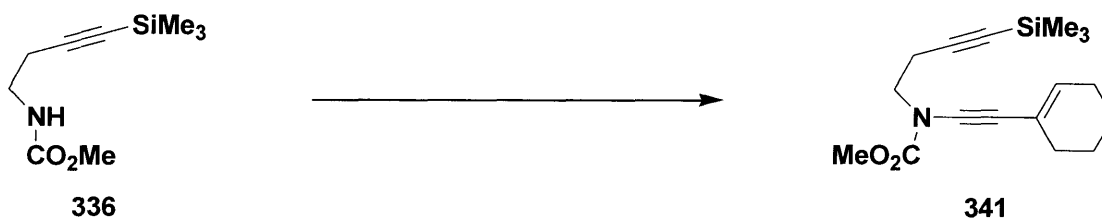




***N*-(Methoxycarbonyl)-*N*-(3-methyl-3-buten-1-ynyl)-4-methoxycarbonyl-3-butynylamine (343).**

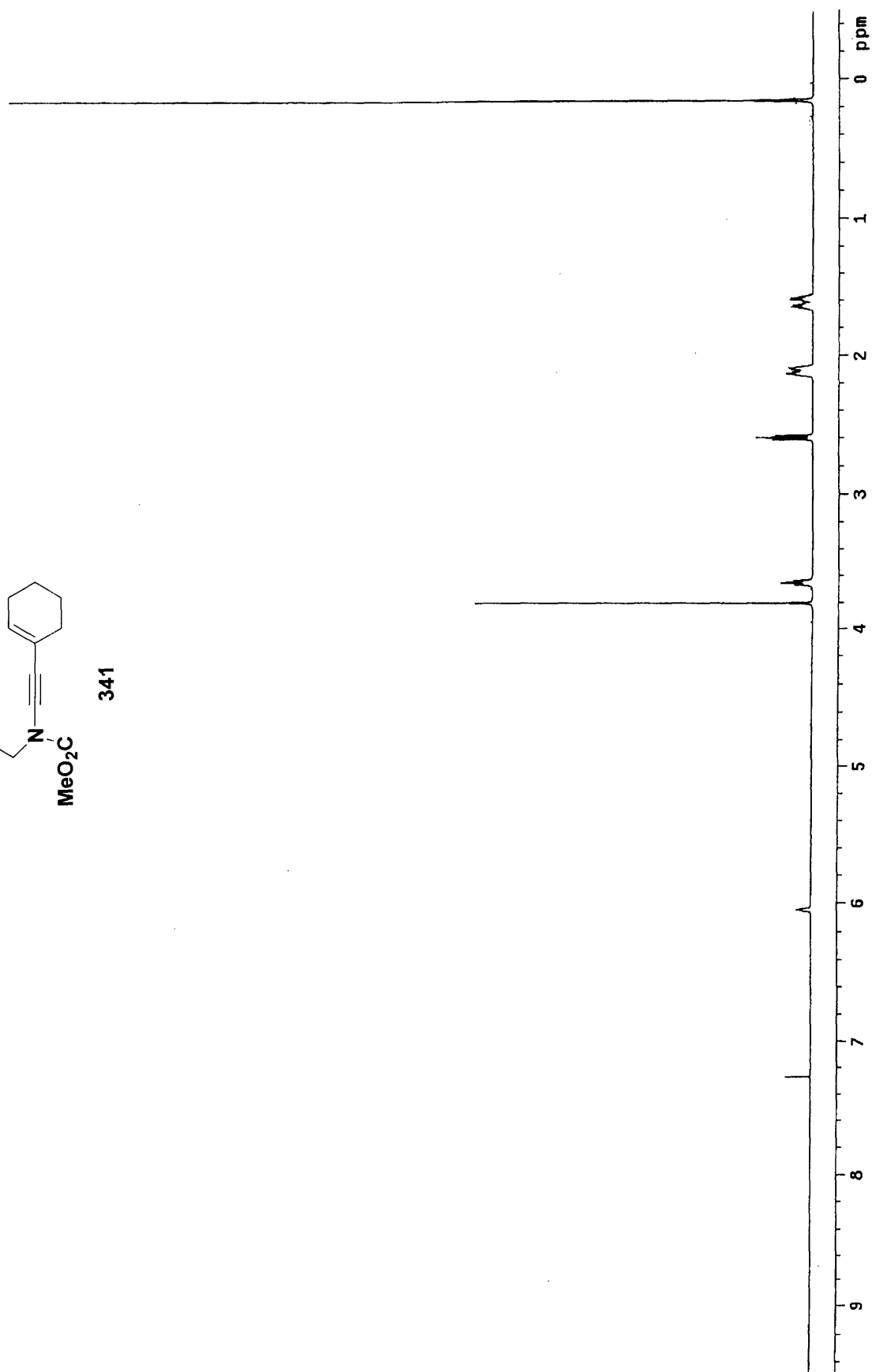
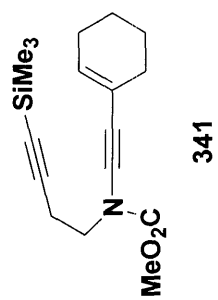
A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with alkyne **342** (0.151 g, 0.790 mmol) and 7.9 mL of THF. The solution was cooled at $-78\text{ }^{\circ}\text{C}$ while 1.0 mL of LiHMDS solution (1.03 M in THF, 1.0 mmol) was added via syringe over 1 min, and the resulting yellow solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 90 min. Methyl chloroformate (0.60 mL, 0.75 g, 7.9 mmol) was added in one portion via syringe, and the reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 3 h. The dry ice-acetone bath was replaced with an ice bath, and the reaction mixture was stirred at $0\text{ }^{\circ}\text{C}$ for 1 h and then diluted with 30 mL of Et_2O . The solution was extracted with 15 mL of a 2:1 mixture of conc NH_4OH solution and satd NaCl solution, and the aqueous layer was extracted with two 10-mL portions of Et_2O . The combined organic layers were washed with 20 mL of satd NaCl solution, dried over MgSO_4 , filtered, and concentrated to provide 0.375 g of a mixture of yellow oil and white needles. Column chromatography on 30 g silica gel (elution with 15% EtOAc-hexanes) provided 0.134 g (68%) of ynamide **343** as a colorless oil: IR (neat) 2956, 2241, 2154, 1729, 1692, 1613, and 1440 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.16 (s, 1H), 5.11 (s, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 3.68 (t, $J = 7.2\text{ Hz}$, 2H), 2.68 (t, $J = 7.2\text{ Hz}$, 2H), and 1.85 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 155.2, 153.8, 126.1, 120.1, 85.0, 81.1, 74.3, 72.4, 54.3, 52.7, 47.9, 23.6, and 18.2; HRMS-ESI m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_4$, 250.1074; found, 250.1069.

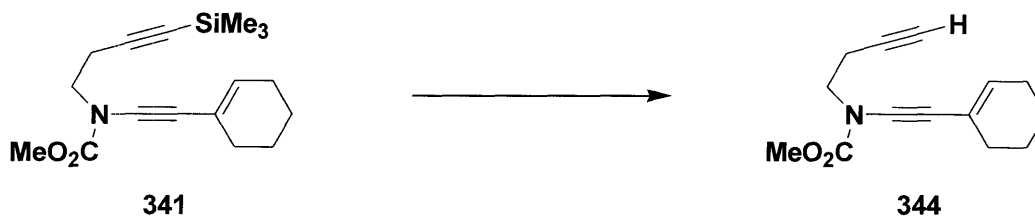




***N*-(Methoxycarbonyl)-*N*-[2-(1-cyclohexenyl)-ethynyl]-4-(trimethylsilyl)-3-butynylamine (341).**

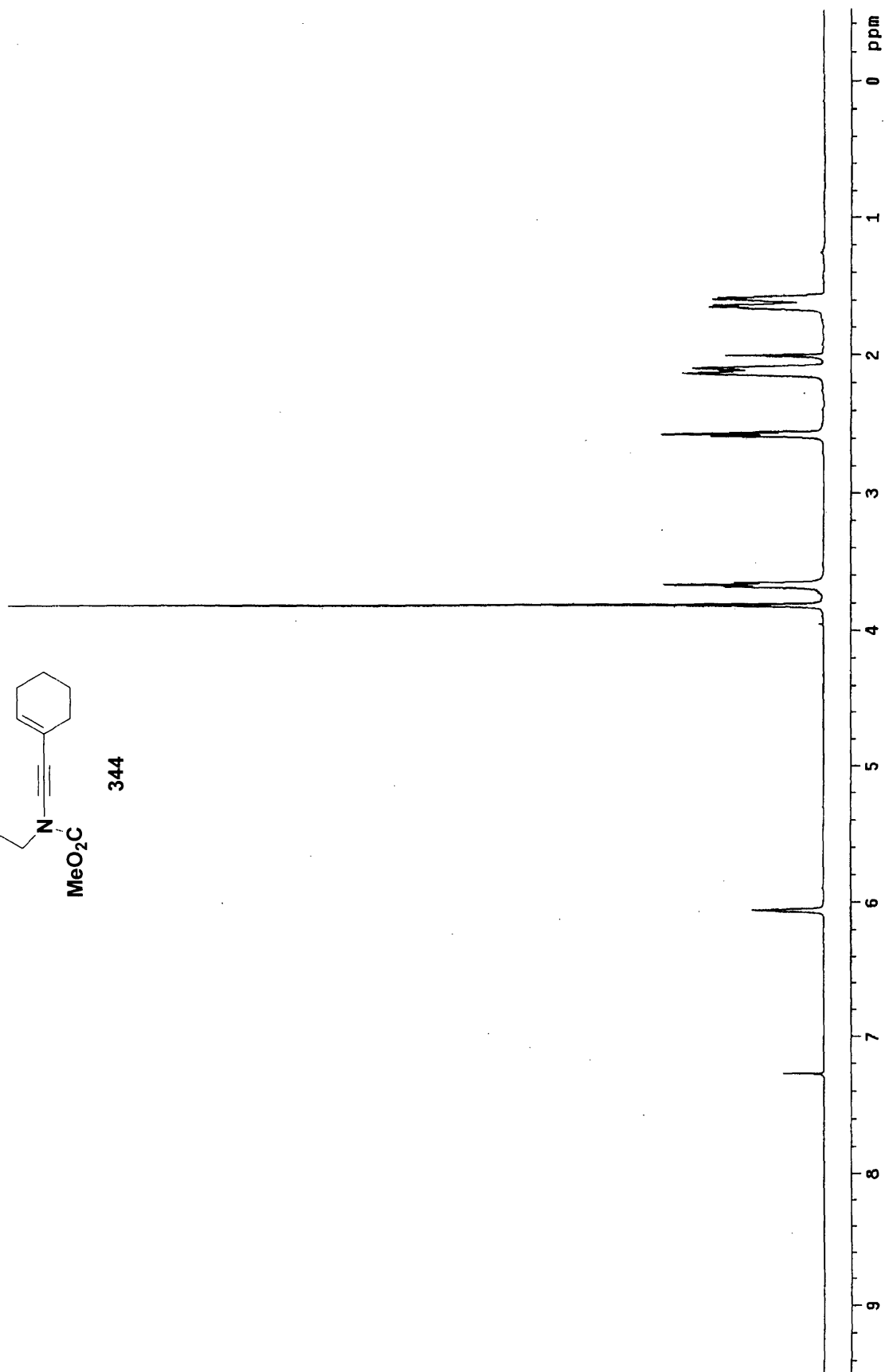
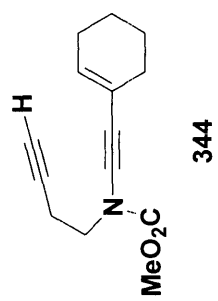
Reaction of a solution of carbamate **336** (0.617 g, 3.10 mmol) in 14 mL of pyridine with KHMDS (3.5 mL, 0.90 M in THF, 3.2 mmol), CuI (0.600 g, 3.15 mmol) in 6 mL of pyridine, and 1-bromo-2-(1-cyclohexenyl)acetylene (**230**) (10.5 mL, 0.59 M in benzene, 6.2 mmol) according to the general procedure gave 1.266 g of a dark red oil. Column chromatography on 140 g of silica gel (gradient elution with 0–1% EtOAc-hexanes) provided 0.572 g (61%) of ynamide **341** as a pale yellow oil: IR (neat) 2933, 2239, 2179, 1730, and 1441 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.01 (m, 1H), 3.76 (s, 1H), 3.61 (t, $J = 7.6$ Hz, 2H), 2.55 (t, $J = 7.6$ Hz, 2H), 2.04–2.11 (m, 4H), 1.60 (m, 2H), 1.55 (m, 2H), and 0.11 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 155.5, 133.8, 120.2, 102.8, 86.7, 79.9, 72.3, 54.1, 49.2, 29.7, 25.8, 22.5, 21.7, 19.3, and 0.1; HRMS-ESI m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{25}\text{NO}_2\text{Si}$, 304.1727; found, 304.1726.

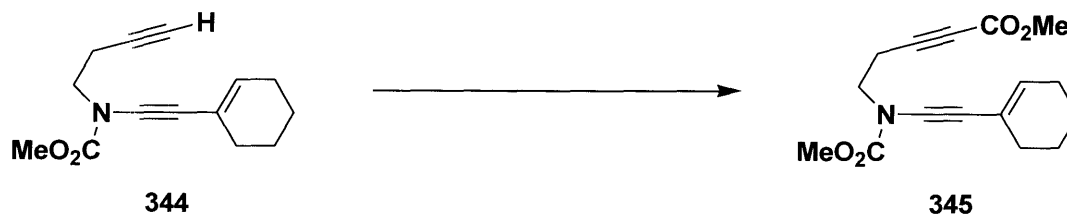




***N*-(Methoxycarbonyl)-*N*-[2-(1-cyclohexenyl)-ethynyl]-3-butynylamine (**344**).**

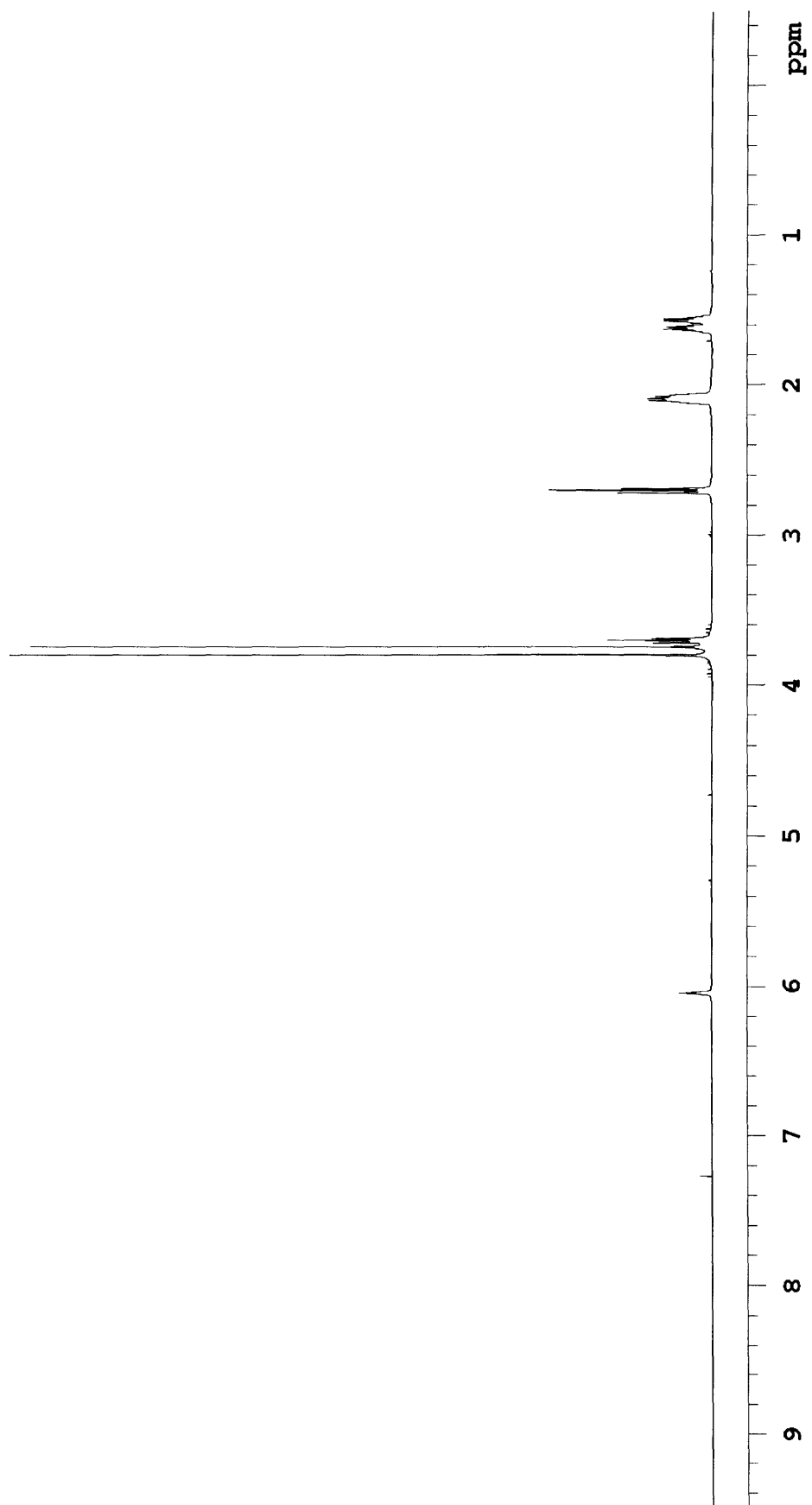
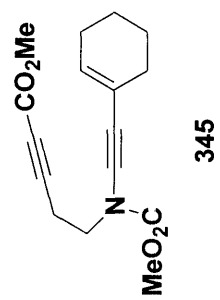
A 100-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with silyl alkyne **341** (0.572 g, 1.88 mmol) and 38 mL of THF. The solution was cooled at 0 °C while 2.1 mL of *n*-Bu₄NF solution (1.0 M in THF, 2.1 mmol) was added via syringe, and the resulting dark red solution was stirred at 0 °C for 10 min. The reaction mixture was diluted with 40 mL of Et₂O and extracted with 40 mL of water. The aqueous layer was extracted with two 25-mL portions of Et₂O, and the combined organic layers were washed with 50 mL of satd NaCl solution, dried over MgSO₄, filtered, and concentrated to provide 0.445 g of a dark red oil. Column chromatography on 30 g silica gel (elution with 5% EtOAc-hexanes) provided 0.387 g (89%) of desilylated alkyne **344** as a pale yellow oil: IR (neat) 3289, 2932, 2239, 2122, 1730, and 1441 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.05 (m, 1H), 3.81 (s, 3H), 3.67 (t, *J* = 7.3 Hz, 2H), 2.57 (dt, *J* = 2.7, 7.3 Hz, 2H), 2.08–2.15 (m, 4H), 2.00 (t, *J* = 2.7 Hz, 1H), 1.64 (m, 2H), and 1.58 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 155.5, 133.9, 120.0, 80.3, 79.5, 72.3, 70.2, 54.1, 48.8, 29.6, 25.7, 22.4, 21.6, and 17.7; GC-MS *m/z*: 231 (M⁺).

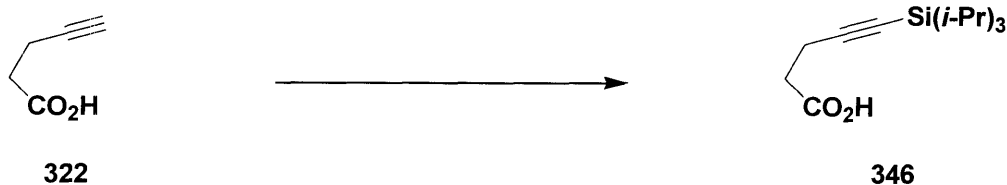




***N*-(Methoxycarbonyl)-*N*-[2-(1-cyclohexenyl)-ethynyl]-4-methoxycarbonyl-3-butynylamine (345).**

A 25-mL round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with alkyne **344** (0.364 g, 1.57 mmol) and 16 mL of THF. The solution was cooled at -78°C while 2.0 mL of LiHMDS solution (1.03 M in THF, 2.1 mmol) was added via syringe over 1 min, and the resulting yellow solution was stirred at -78°C for 2 h. Methyl chloroformate (1.2 mL, 1.5 g, 16 mmol) was then added in one portion via syringe, and the resulting mixture was stirred at -78°C for 3 h. The dry ice-acetone bath was replaced with an ice bath, and the reaction mixture was stirred at 0°C for 1 h and then diluted with 60 mL of Et_2O . The solution was extracted with 30 mL of a 2:1 mixture of conc NH_4OH solution and satd NaCl solution, and the aqueous layer was extracted with two 20-mL portions of Et_2O . The combined organic layers were washed with 50 mL of satd NaCl solution, dried over MgSO_4 , filtered, and concentrated to provide 0.835 g of a mixture of yellow oil and white needles. Column chromatography on 40 g silica gel (elution with 15% EtOAc -hexanes) provided 0.325 g (72%) of ynamide **345** as a colorless oil: IR (neat) 2932, 2241, 1722, 1692, and 1440 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.05 (m, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 3.70 (t, $J = 7.3\text{ Hz}$, 2H), 2.70 (t, $J = 7.3\text{ Hz}$, 2H), 2.09 (m, 4H), 1.62 (m, 2H), and 1.57 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 155.5, 154.0, 134.5, 119.9, 85.3, 79.3, 74.3, 72.7, 54.4, 52.8, 48.1, 29.6, 25.8, 22.5, 21.6, and 18.2; HRMS-ESI m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_4$, 290.1387; found, 290.1374.

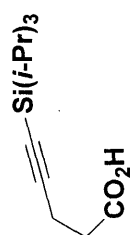




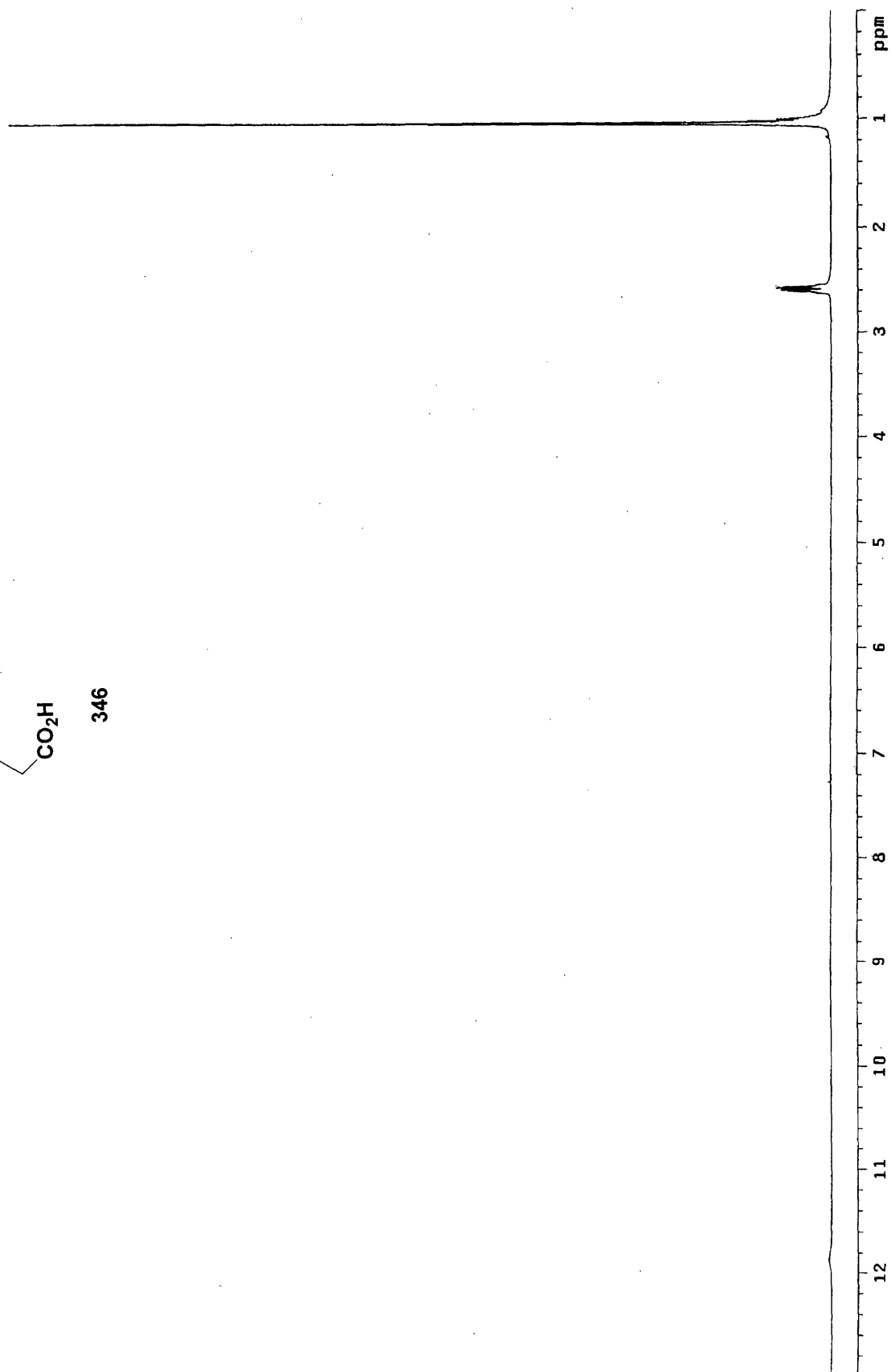
5-(Triisopropylsilyl)-4-pentynoic acid (**346**).

A 1-L, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with 4-pentynoic acid (**322**) (3.522 g, 35.90 mmol) and 300 mL of THF and cooled at $-78\text{ }^{\circ}\text{C}$ while 30 mL of *n*-BuLi solution (2.45 M in hexanes, 74 mmol) was added via syringe over 3 min. The resulting white mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min. Chlorotriisopropylsilane (17 mL, 15 g, 79 mmol) was added via syringe in one portion, the ice bath was removed, and the resulting solution was stirred at rt for 2 h. The reaction mixture was diluted with 100 mL of water and 200 mL of satd NaCl solution, and the aqueous layer was separated and extracted with two 100-mL portions of Et₂O. The combined organic layers were dried over MgSO₄, filtered, and concentrated to give 17.268 g of a yellow oil.

A 500-mL, round-bottomed flask equipped with an argon inlet adapter was charged with the yellow oil from the previous step in 160 mL of THF, 40 mL of methanol, and 40 mL of water. Potassium carbonate (24.8 g, 180 mmol) was added in one portion and the reaction mixture was vigorously stirred for 1 h. The resulting suspension was then diluted with 200 mL of CH₂Cl₂ and 100 mL of satd NaCl solution, and 2 M HCl was added dropwise to adjust the pH to 2 (ca. 150 mL of 2 M HCl was added). The resulting mixture was diluted with 100 mL of satd NaCl solution, and the aqueous layer was separated and extracted with two 200-mL portions of CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered, and concentrated to give 18.138 g of a dark yellow oil. Removal of triisopropylsilanol was achieved by four successive purifications via column chromatography on 150 g silica gel (elution with 5% EtOAc-hexanes-1% AcOH) to provide 2.135 g (23%) of acid **346** as a colorless oil: IR (neat) 3037, 2943, 2865, 2177, 1712, 1463, and 1433 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 11.86 (br s, 1H), 2.59 (m, 4H), 1.05 (d, *J* = 5.0 Hz, 18H), and 1.03 (sept, *J* = 5.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 178.8, 106.4, 81.8, 34.1, 18.7, 15.8, and 11.4; HRMS-ESI *m/z*: [M+Na]⁺ calcd for C₁₄H₂₆O₂Si, 277.1594; found, 277.1593.



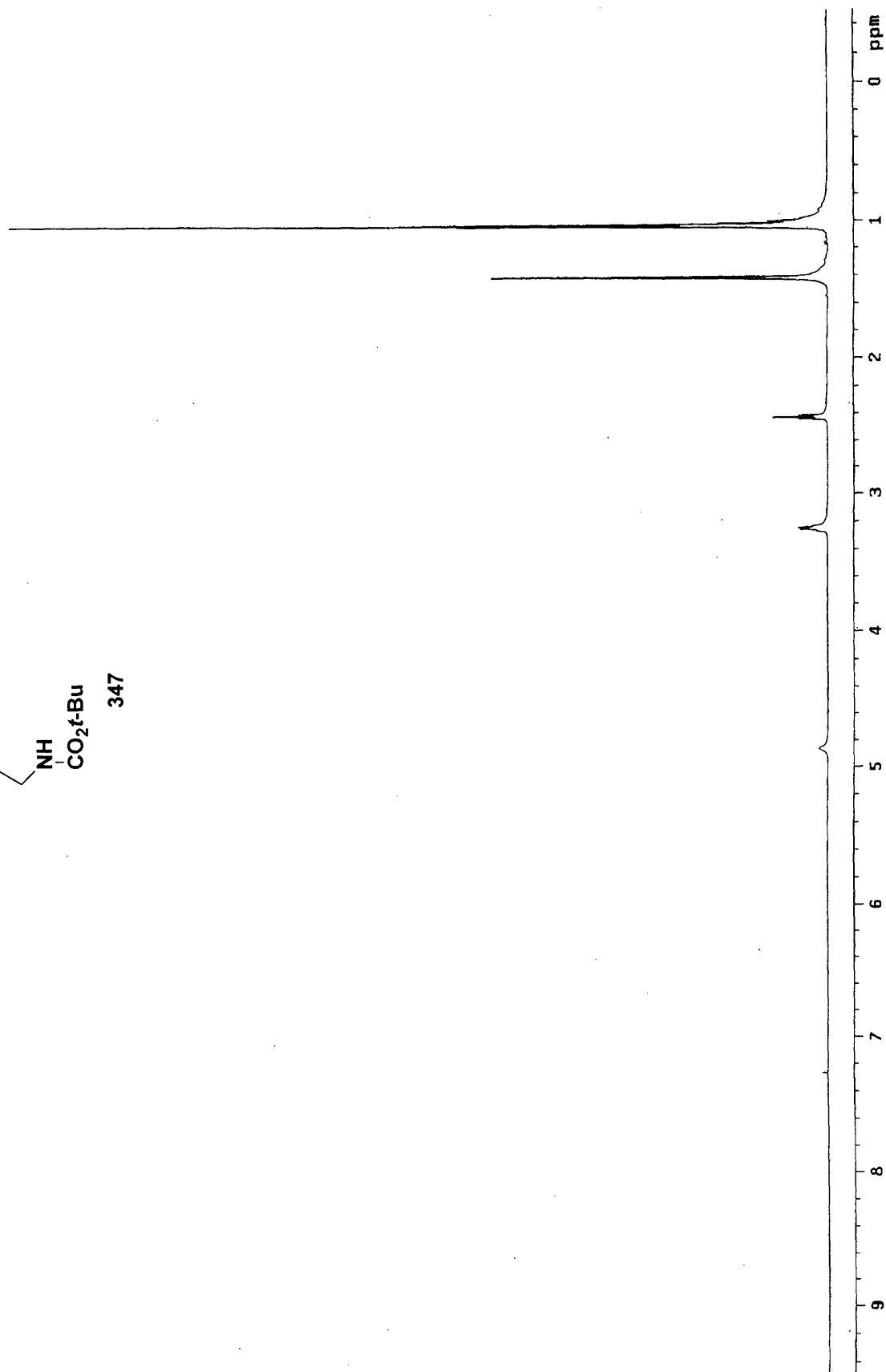
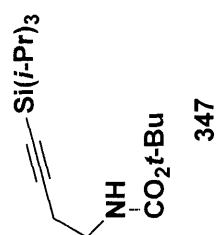
346

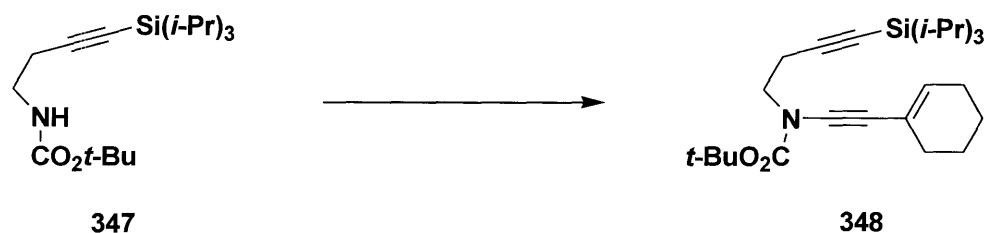




***N*-(*tert*-Butoxycarbonyl)-4-(triisopropylsilyl)-3-butyne-1-amine (347).**

A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and reflux condenser fitted with an argon inlet adapter was charged with acid **346** (2.135 g, 8.391 mmol), 12 mL of toluene, and triethylamine (1.17 mL, 0.849 g, 8.39 mmol). Diphenylphosphoryl azide (1.81 mL, 2.31 g, 8.40 mmol) was added via syringe over 2 min, and the resulting solution was heated at 80 °C (bath temperature) until bubbling ceased (2 h). After the oil bath was warmed to 90 °C, *tert*-butanol (7.8 mL, 6.0 g, 84 mmol) was added and the resulting mixture was heated at reflux for 23 h. The solution was allowed to cool to room temperature, and the reaction mixture was concentrated onto 8 g of silica gel which was applied to a column of 180 g of silica gel (gradient elution with 2–20% EtOAc-hexanes) for purification to provide 0.838 g (31%) of carbamate **347** as a pale yellow oil: IR (neat) 3357, 2943, 2866, 2173, 1694, 1511, and 1463 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.87 (br s, 1H), 3.25 (dt, *J* = 6.1, 6.6 Hz, 2H), 2.43 (t, *J* = 6.6 Hz, 2H), 1.42 (s, 9H), 1.04 (d, *J* = 5.0 Hz, 18H), and 1.03 (sept, *J* = 5.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 155.9, 105.8, 82.5, 79.4, 39.7, 28.5, 21.4, 18.8, and 11.4; HRMS-ESI *m/z*: [M+Na]⁺ calcd for C₁₈H₃₅NO₂Si, 348.2329; found, 348.2314.

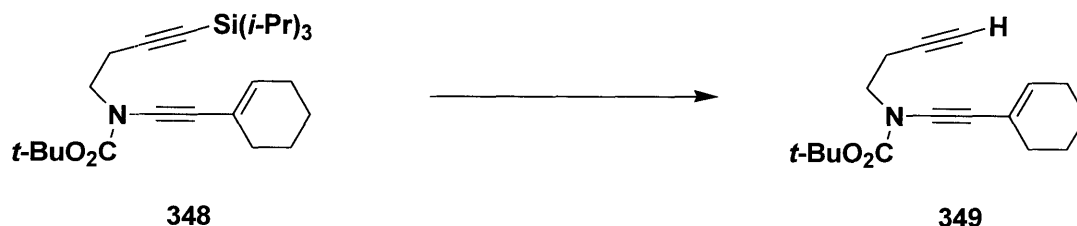




***N*-(*tert*-Butoxycarbonyl)-*N*-[2-(1-cyclohexenyl)-ethynyl]-4-(triisopropylsilyl)-3-butynylamine (**348**).**

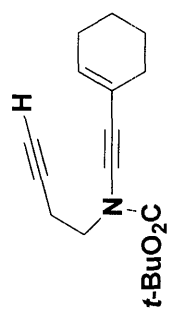
Reaction of a solution of carbamate **347** (0.253 g, 0.777 mmol) in 3.1 mL of pyridine with KHMDS (0.86 mL, 0.91 M in THF, 0.78 mmol), CuI (0.148 g, 0.777 mmol) in 1.6 mL of pyridine, and 1-bromo-2-(1-cyclohexenyl)acetylene (**230**) (2.6 mL, 0.60 M in benzene, 1.6 mmol) according to the general procedure gave 0.478 g of a dark red oil. Column chromatography on 40 g of silica gel (gradient elution with 0–5% EtOAc-hexanes) provided 0.160 g (48%) of ynamide **348** as a pale yellow oil: IR (neat) 2940, 2865, 2238, 2175, 1716, and 1463 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.93 (br s, 1H), 3.58 (t, $J = 7.8$ Hz, 2H), 2.59 (t, $J = 7.8$ Hz, 2H), 2.05–2.12 (m, 4H), 1.62 (m, 2H), 1.57 (m, 2H), 1.48 (s, 9H), 1.04 (d, $J = 5.8$ Hz, 18H), and 1.03 (sept, $J = 5.8$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 153.8, 131.5, 120.4, 104.5, 82.2, 82.2, 80.7, 72.3, 48.2, 29.5, 28.0, 25.6, 22.5, 21.7, 19.3, 18.6, and 11.3; HRMS-ESI m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{26}\text{H}_{43}\text{NO}_2\text{Si}$, 452.2955; found, 452.2958.



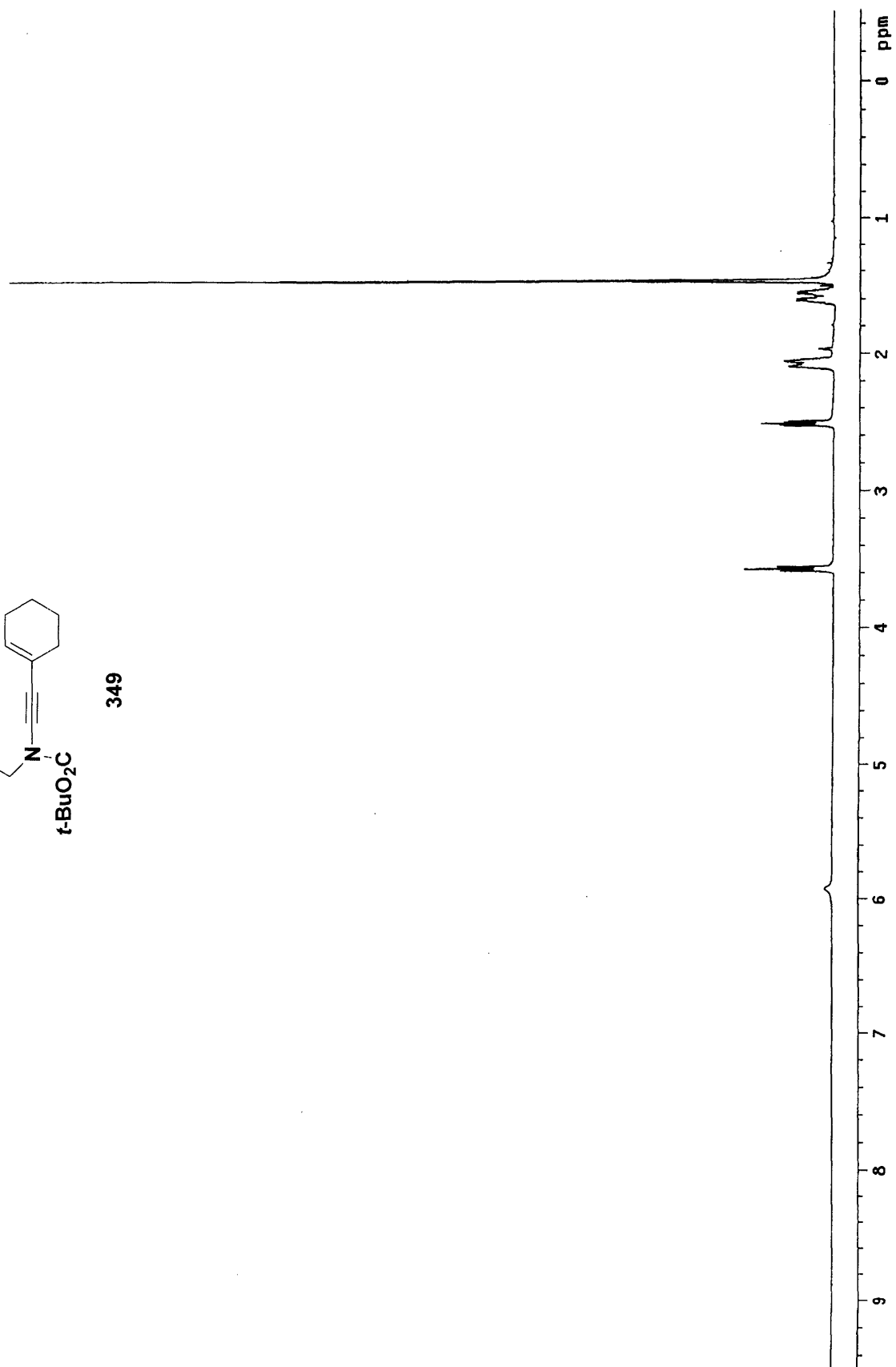


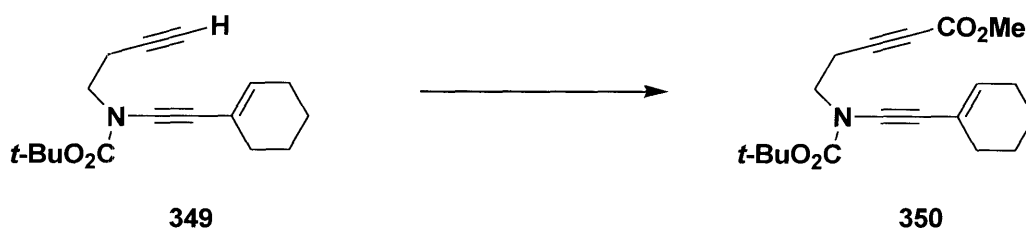
***N*-(*tert*-Butoxycarbonyl)-*N*-[2-(1-cyclohexenyl)-ethynyl]-3-butynylamine (**349**).**

A 100-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with silyl alkyne **348** (0.687 g, 1.60 mmol) and 50 mL of THF and cooled at 0 °C while 1.8 mL of *n*-Bu₄NF solution (1.0 M in THF, 1.8 mmol) was added via syringe. The resulting light brown solution was stirred at 0 °C for 20 min and then diluted with 50 mL of Et₂O and extracted with 50 mL of water. The aqueous layer was extracted with two 25-mL portions of Et₂O, and the combined organic layers were washed with 100 mL of satd NaCl solution, dried over MgSO₄, filtered, and concentrated to provide 0.735 g of a deep yellow oil. Column chromatography on 60 g of silica gel (elution with 2% EtOAc-hexanes) provided 0.345 g (79%) of desilylated alkyne **349** as a pale yellow oil: IR (neat) 3290, 2933, 2237, 2122, 1722, and 1449 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.92 (br s, 1H), 3.57 (t, *J* = 7.5 Hz, 2H), 2.51 (dt, *J* = 2.7, 7.5 Hz, 2H), 2.04–2.10 (m, 4H), 1.96 (t, *J* = 2.7 Hz, 1H), 1.60 (m, 2H), 1.55 (m, 2H), and 1.47 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 153.9, 131.8, 120.4, 82.4, 80.7, 80.6, 72.3, 70.1, 47.8, 29.6, 28.1, 25.7, 22.5, 21.7, and 18.0; HRMS-ESI *m/z*: [M+Na]⁺ calcd for C₁₇H₂₃NO₂, 296.1621; found, 296.1625.



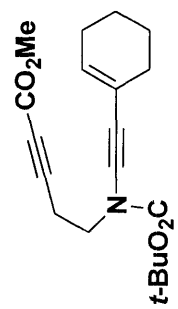
349



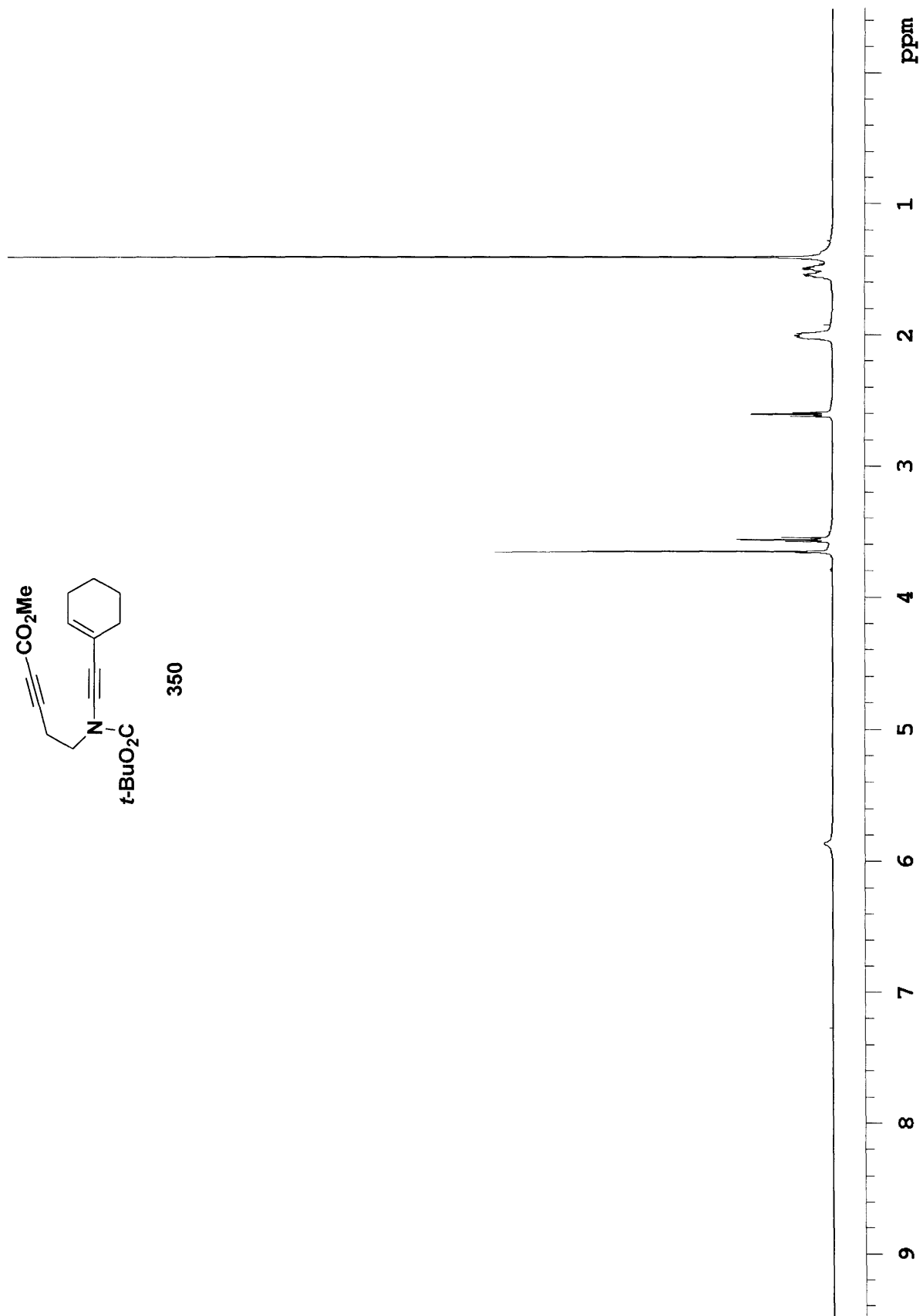


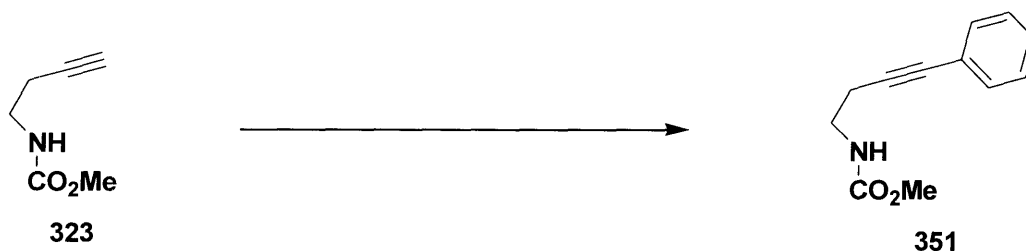
***N*-(*tert*-Butoxycarbonyl)-*N*-[2-(1-cyclohexenyl)-ethynyl]-4-methoxycarbonyl-3-butynylamine (**350**).**

A 10-mL, pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with hexamethyldisilazane (0.37 mL, 0.28 g, 1.8 mmol) and 3 mL of THF. The solution was cooled at 0 °C while 0.68 mL of *n*-BuLi solution (2.40 M in hexanes, 1.6 mmol) was added via syringe over 2 min and allowed to stir at 0 °C for 30 min. A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with alkyne **349** (0.345 g, 1.26 mmol) and 9 mL of THF. The solution was cooled at –78 °C while the LiHMDS solution prepared as described above was added via cannula over 3 min (0.6-mL THF rinse). The resulting yellow solution was stirred at –78 °C for 2 h. Methyl chloroformate (0.97 mL, 1.2 g, 13 mmol) was added in one portion via syringe, and the reaction mixture was stirred at –78 °C for 3 h. The dry ice-acetone bath was replaced with an ice bath, and the reaction mixture was stirred at 0 °C for 1 h and then diluted with 60 mL of Et₂O. The solution was extracted with 30 mL of a 2:1 mixture of conc NH₄OH solution and satd NaCl solution, and the aqueous layer was extracted with two 20-mL portions of Et₂O. The combined organic layers were washed with 50 mL of satd NaCl solution, dried over MgSO₄, filtered, and concentrated to provide 0.965 g of a mixture of yellow oil and white needles. Column chromatography on 90 g silica gel (elution with 5% EtOAc-hexanes) provided 0.249 g (60%) of ynamide **350** as a colorless oil: IR (neat) 2933, 2241, 1720, and 1435 cm^{–1}; ¹H NMR (500 MHz, CDCl₃) δ 5.87 (br s, 1H), 3.65 (s, 3H), 3.56 (t, *J* = 7.2 Hz, 2H), 2.61 (t, *J* = 7.2 Hz, 2H), 2.00 (m, 4H), 1.55 (m, 2H), 1.49 (m, 2H), and 1.41 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 153.7, 153.5, 131.9, 120.1, 85.4, 82.5, 80.2, 74.0, 72.4, 52.5, 46.8, 29.4, 27.9, 25.5, 22.3, 21.6, and 18.1; HRMS-ESI *m/z*: [M+Na]⁺ calcd for C₁₉H₂₅NO₄, 354.1676; found, 354.1679.



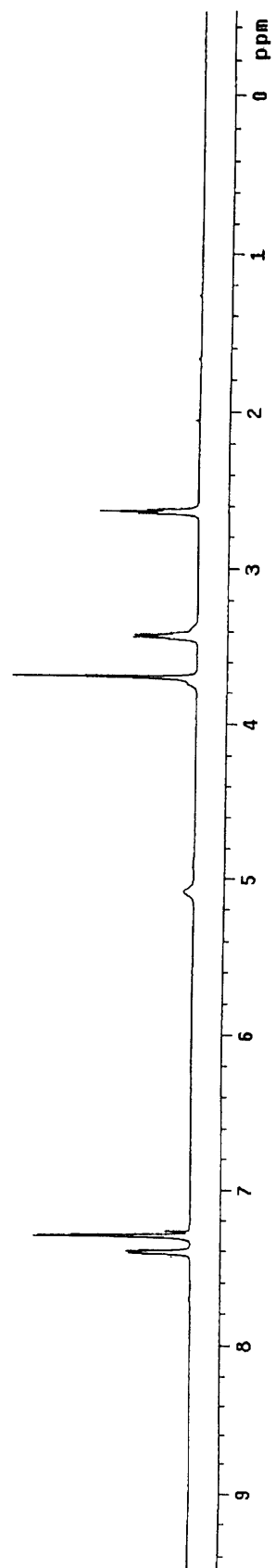
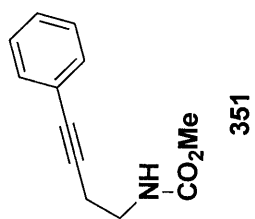
350





***N*-(Methoxycarbonyl)-4-phenyl-3-butynylamine (351).**

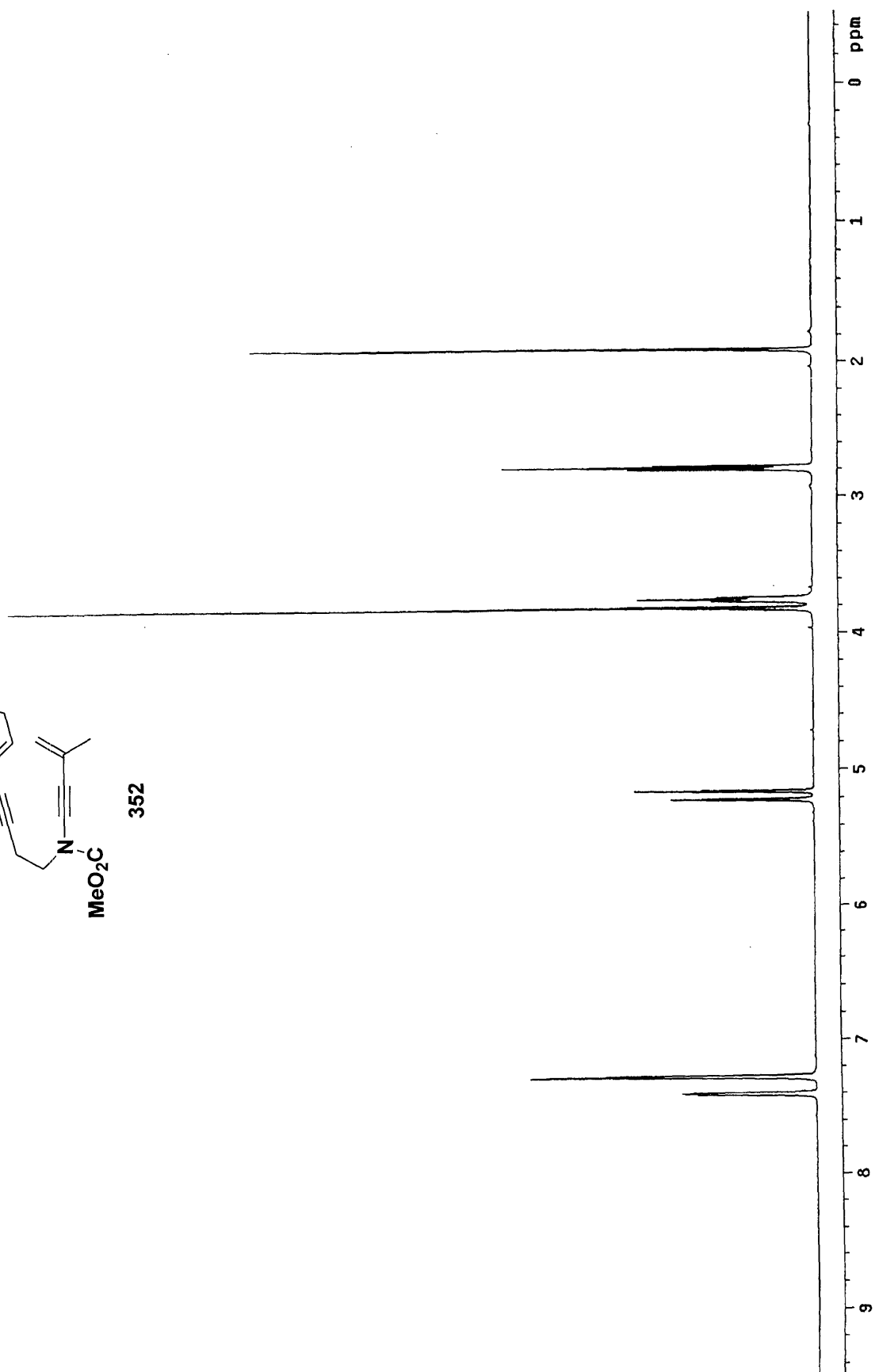
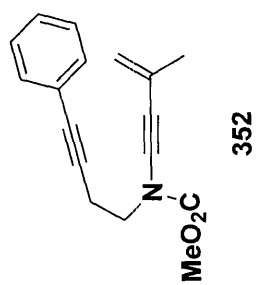
A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ (0.130 g, 0.185 mmol) and CuI (0.071 g, 0.37 mmol), and a solution of alkyne **323** (0.787 g, 6.19 mmol) in 10 mL of THF was added via cannula in one portion (2.1-mL piperidine rinse). Iodobenzene (1.04 mL, 1.90 g, 9.29 mmol) was added in one portion via syringe and the resulting yellow reaction mixture was stirred at rt for 3 h. The reaction mixture was diluted with 30 mL of Et_2O and filtered through a column of silica gel (10 x 3 cm) with the aid of 300 mL of Et_2O . Concentration of the filtrate afforded 1.968 g of a red oil. Column chromatography on 150 g of silica gel (gradient elution with 10–20% EtOAc-hexanes) provided 1.153 g (92%) of arenyne **351** as a pale orange solid: mp 58–60 °C; IR (film) 3333, 2947, 2233, 1704, 1598, 1530, 1490, 1442, and 1263 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.41 (m, 2H), 7.30 (m, 3H), 4.90 and 5.08 (NH rotamers, br s, 1H), 3.69 (s, 3H), 3.43 (dt, $J = 6.1, 6.4$ Hz, 2H), and 2.63 (t, $J = 6.1$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 157.1, 131.8, 128.5, 128.2, 123.5, 87.0, 82.3, 52.4, 40.1, and 21.1.

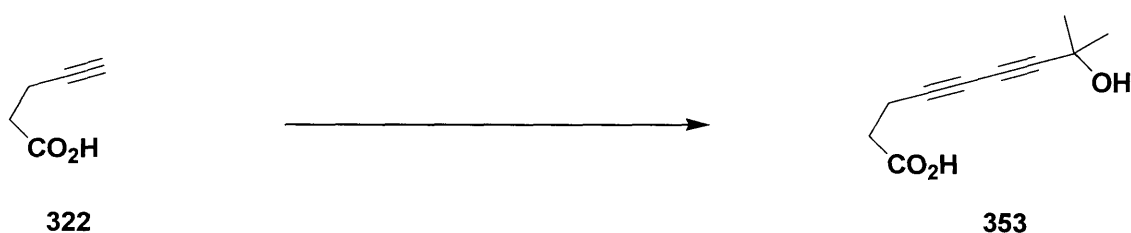




***N*-(Methoxycarbonyl)-*N*-(3-methyl-3-buten-1-ynyl)-4-phenyl-3-butynylamine (**352**).**

Reaction of a solution of carbamate **351** (0.567 g, 2.79 mmol) in 11 mL of pyridine with KHMDS (3.1 mL, 0.91 M in THF, 2.8 mmol), CuI (0.533 g, 2.80 mmol) in 6 mL of pyridine, and 1-bromo-3-methyl-3-buten-1-yne (9.3 mL, 0.60 M in benzene, 5.6 mmol) according to the general procedure gave 0.913 g of a dark red oil. Column chromatography on 80 g of silica gel (gradient elution with 0–5% EtOAc-hexanes) provided 0.344 g (46%) of ynamide **352** as a yellow oil: IR (neat) 2954, 2235, 1731, 1613, 1598, and 1442 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.41 (m, 2H), 7.28 (m, 3H), 5.21 (s, 1H), 5.15 (s, 1H), 3.81 (s, 3H), 3.76 (t, $J = 7.3$ Hz, 2H), 2.79 (t, $J = 7.3$ Hz, 2H), and 1.91 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 155.5, 131.7, 128.3, 128.0, 126.4, 123.5, 119.8, 85.6, 82.4, 81.8, 72.2, 54.2, 49.2, 23.8, and 19.0; HRMS-ESI m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{17}\text{NO}_2$, 268.1332; found, 268.1331.

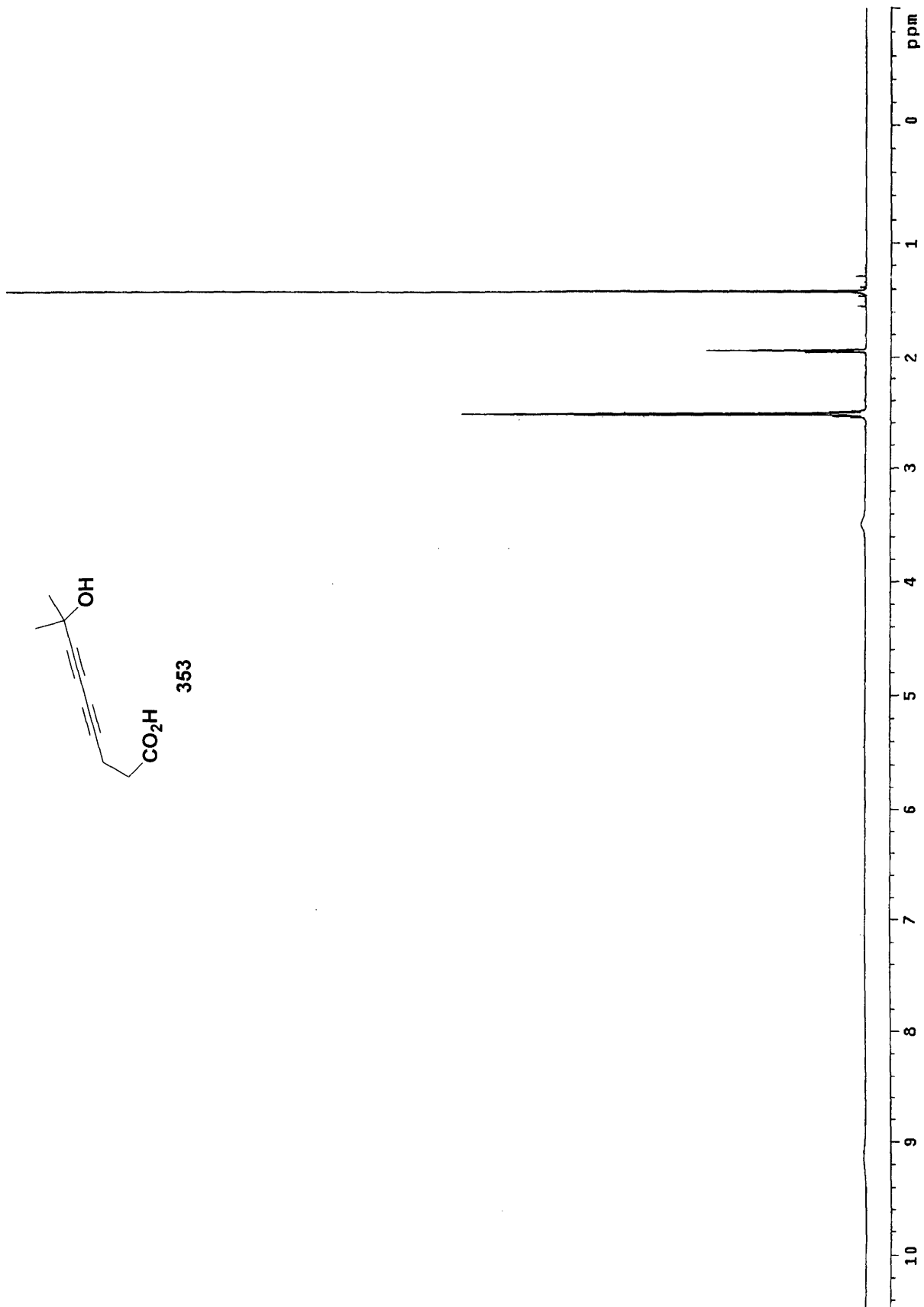


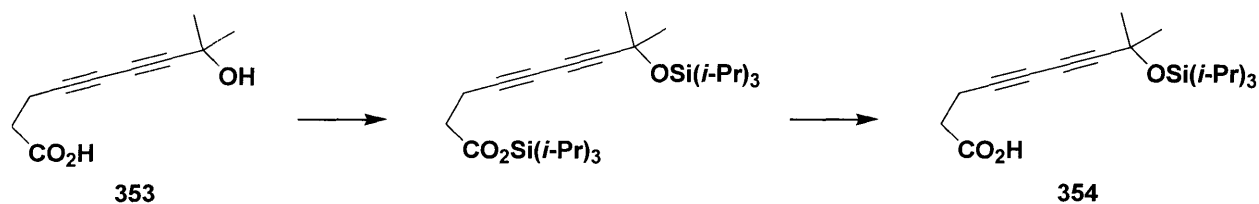


8-Hydroxy-8-methyl-nona-4,6-dienoic acid (**353**).

A 200-mL, three-necked, round-bottomed flask equipped with two glass stoppers and an addition funnel fitted with an argon inlet adapter was charged with CuCl (0.023 g, 0.23 mmol), $\text{NH}_2\text{OH}\cdot\text{HCl}$ (0.112 g, 1.61 mmol), 22 mL of methanol, and 20 mL of aqueous ethylamine (70% wt in H_2O) solution. The reaction mixture was cooled at 0 °C while 4-pentynoic acid (**322**) (4.350 g, 44.34 mmol) was added in one portion. 1-Bromo-3-hydroxy-3-methylbutyne (**234**) (6.896 g, 42.30 mmol) was added dropwise via the addition funnel over 15 min, and the resulting pale yellow solution was stirred at 0 °C for 20 min. The solution was diluted with 100 mL of water, 20 mL of conc HCl, and extracted with twenty-five 50-mL portions of CH_2Cl_2 . The combined organic phases were concentrated to a volume of ca. 150 mL, washed with 100 mL of satd NaCl solution, dried over MgSO_4 , filtered, and concentrated to give 6.164 g of a white solid. Trituration of the crude material with two 150-mL portions of hexanes (heated to boiling point) afforded 3.040 g (40%) of diynoic acid **353** as a white solid: mp 129–131 °C (lit.²⁰³ mp 132 °C); IR (film) 3406, 2983, 2255, 1726, and 1363 cm^{-1} ; ^1H NMR (500 MHz, CD_3CN) δ 9.13 (br s, 1H), 3.49 (br s, 1H), 2.52 (m, 4H), and 1.42 (s, 6H); ^{13}C NMR (125 MHz, CD_3CN) δ 173.5, 82.9, 81.3, 67.0, 65.8, 65.5, 33.2, 31.7, and 15.9; HRMS-ESI m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{10}\text{H}_{12}\text{O}_3$, 203.0679; found, 203.0684.

²⁰³ Prevost, S.; Meier, J.; Chodkiewicz, W.; Cadiot, P.; Willemart, A. *Bull. Soc. Chim. Fr.* **1961**, 2171.

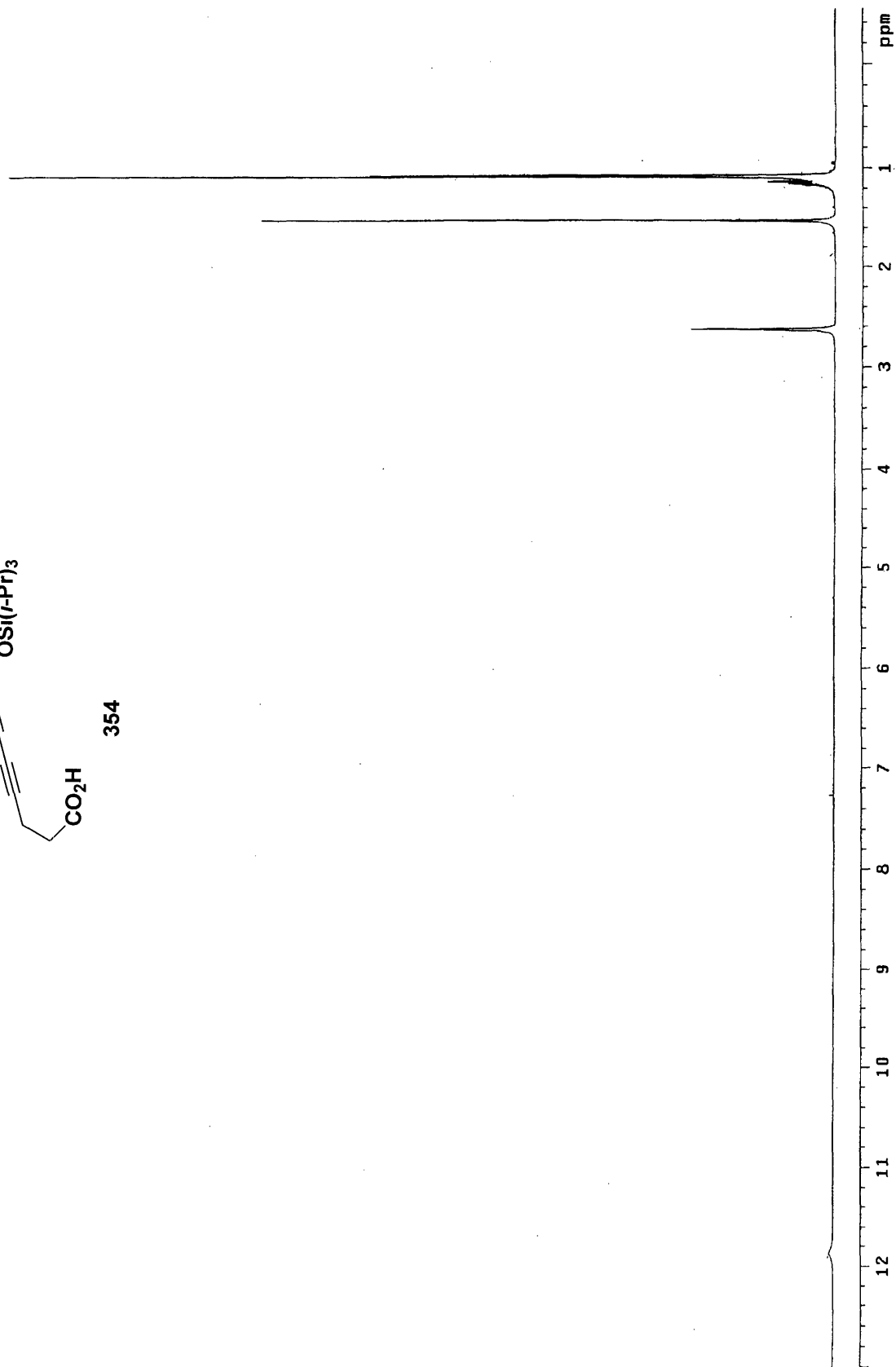
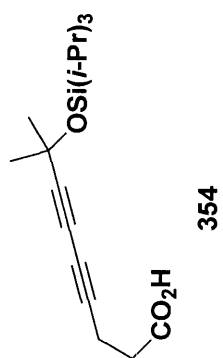


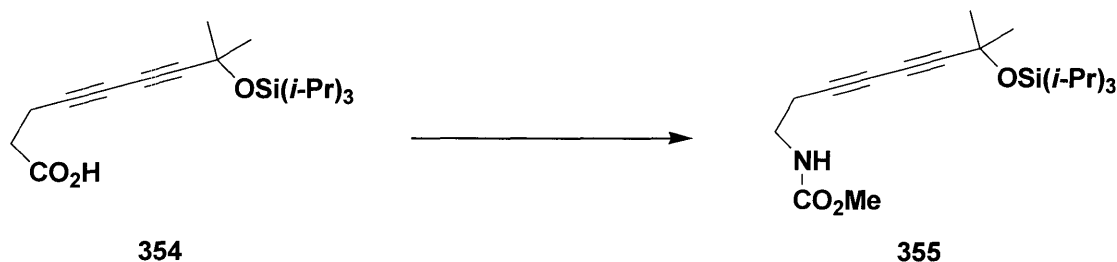


8-(Triisopropylsiloxy)-8-methyl-nona-4,6-diynoic acid (**354**).

A 50-mL, three-necked, round-bottomed flask equipped with two rubber septa and an argon inlet adapter was charged with acid **353** (1.550 g, 8.602 mmol) and 25 mL of CH₂Cl₂. The resulting suspension was cooled at 0 °C while 2,6-lutidine (3.0 mL, 2.7 g, 26 mmol) was added in one portion via syringe, and the resulting homogeneous solution was treated with triisopropylsilyl triflate (5.8 mL, 6.6 g, 22 mmol) via syringe over 3 min. The ice bath was removed and the reaction mixture was allowed to stir at rt for 18 h. The resulting solution was diluted with 50 mL of Et₂O, washed with 20 mL of water, 20 mL of 3% HCl, and 20 mL of satd NaCl solution, dried over MgSO₄, filtered, and concentrated to give 4.832 g of a yellow oil.

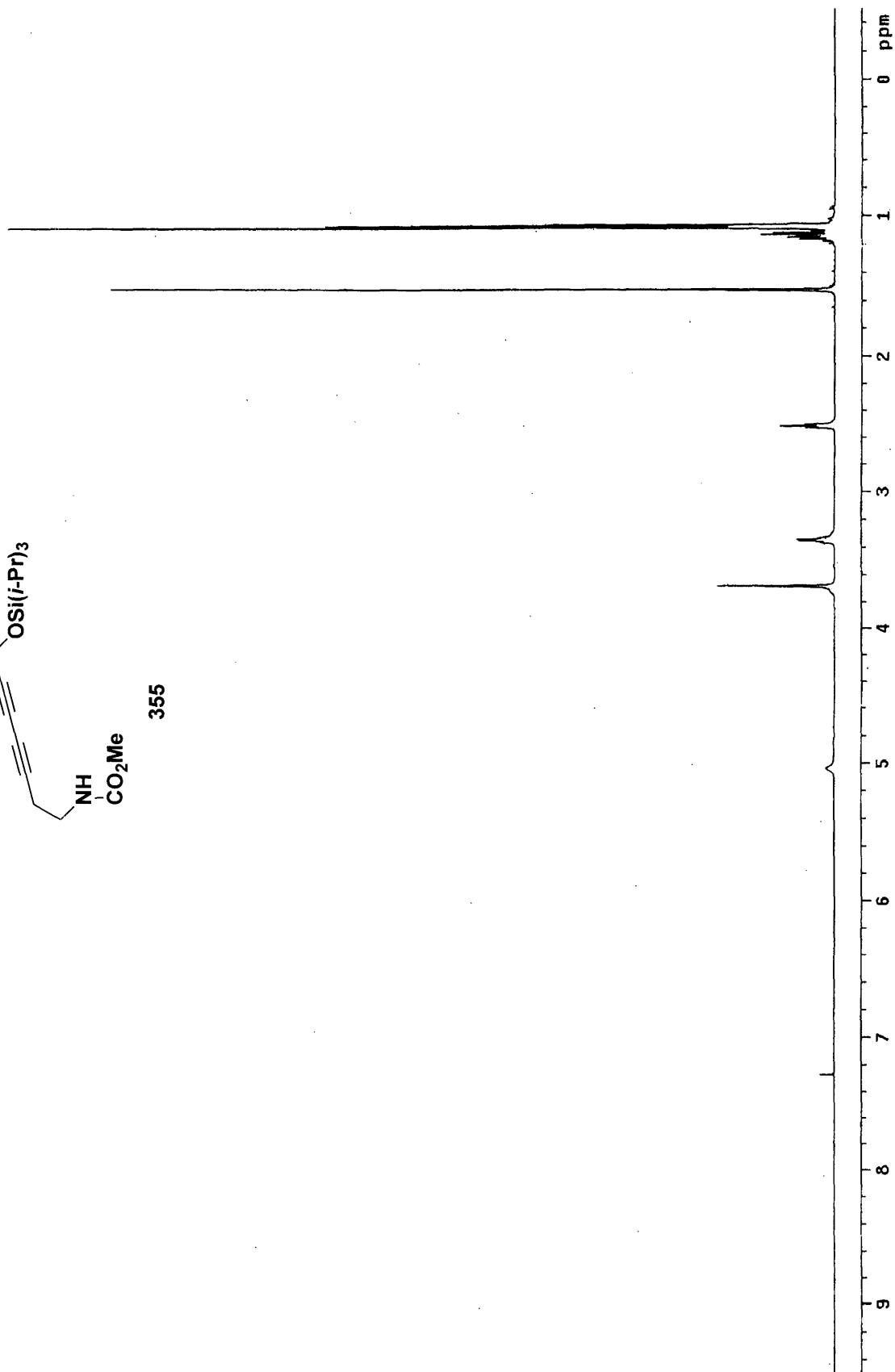
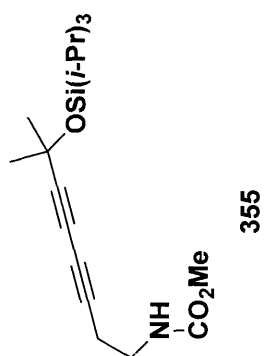
A 100-mL, round-bottomed flask equipped with an argon inlet adapter was charged with a solution of the yellow oil from the previous step in 35 mL of methanol, 10 mL of THF, and 10 mL of water. Potassium carbonate (5.9 g, 43 mmol) was added in one portion, and the reaction mixture was vigorously stirred for 1 h. The resulting suspension was diluted with 100 mL of CH₂Cl₂ and 20 mL of satd NaCl solution, and 10% HCl was added dropwise to adjust the pH to 2 (ca. 55 mL of 10% HCl was added). The resulting mixture was diluted with 20 mL of satd NaCl solution, and the aqueous layer was separated and extracted with 50 mL of CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered, and concentrated to give 4.766 g of a yellow oil. Column chromatography on 140 g of silica gel (elution with 15% EtOAc-hexanes containing 0.1% AcOH) provided 2.688 g (93% overall from **353**) of acid **354** as white solid: mp 49–50 °C; IR (film) 3037, 2944, 2867, 2255, 1715, 1463, and 1432 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 11.88 (br s, 1H), 2.64 (m, 4H), 1.53 (s, 6H), 1.13 (sept, *J* = 6.6 Hz, 3H), and 1.08 (d, *J* = 6.6 Hz, 18H); ¹³C NMR (125 MHz, CDCl₃) δ 178.2, 81.9, 78.4, 67.6, 66.6, 65.7, 33.1, 33.0, 18.5, 15.2, and 13.2; HRMS-ESI *m/z*: [M+Na]⁺ calcd for C₁₉H₃₂O₃Si, 359.2013; found, 359.2007.

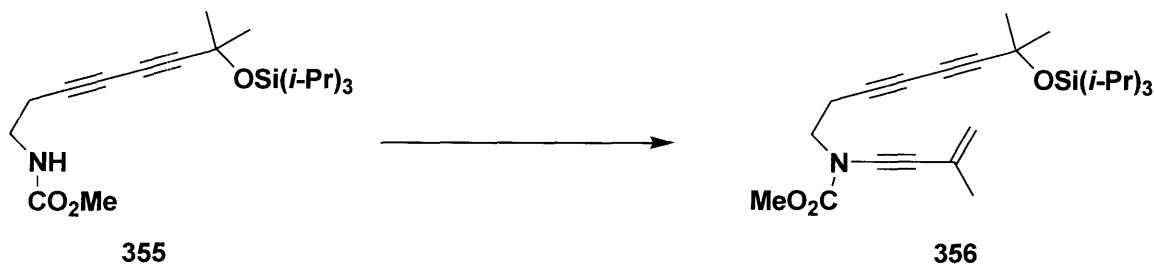




***N*-(Methoxycarbonyl)-7-(triisopropylsiloxy)-7-methyl-octa-3,5-diynylamine (**355**).**

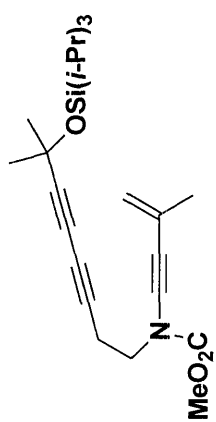
A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and reflux condenser fitted with an argon inlet adapter was charged with acid **354** (1.068 g, 3.173 mmol), 4.6 mL of toluene, and triethylamine (0.45 mL, 0.33 g, 3.2 mmol). Diphenylphosphoryl azide (0.69 mL, 0.88 g, 3.2 mmol) was added via syringe over 1 min, and the resulting solution was heated at 80 °C (bath temperature) until bubbling ceased (2 h). The oil bath was cooled to 50 °C, methanol (1.3 mL, 1.0 g, 32 mmol) was added, and the resulting mixture was stirred at 50 °C for 13 h. The resulting mixture was allowed to cool to room temperature and the toluene and methanol were removed by rotary evaporation at rt and 20 mmHg. The resulting orange-brown oil was diluted with 20 mL of Et₂O and 20 mL of water, and the aqueous phase was extracted with four 100-mL portions of Et₂O. The combined organic phases were washed with 50 mL of satd NaCl solution, dried over MgSO₄, filtered, and concentrated to give 1.142 g of a pale orange solid. Column chromatography on 80 g of silica gel (gradient elution with 10–20% EtOAc-hexanes) provided 1.009 g (87%) of carbamate **355** as a white solid: mp 55–56 °C; IR (film) 3306, 2944, 2866, 2249, 1692, 1563, and 1462 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.04 (br s, 1H), 3.68 (s, 3H), 3.34 (app q, *J* = 6.4 Hz, 2H), 2.51 (t, *J* = 6.4 Hz, 2H), 1.52 (s, 6H), 1.12 (sept, *J* = 6.4 Hz, 3H), and 1.07 (d, *J* = 6.4 Hz, 18H); ¹³C NMR (125 MHz, CDCl₃) δ 157.0, 81.8, 78.0, 67.5, 66.6, 66.4, 52.4, 39.7, 33.1, 21.1, 18.5, and 13.1; HRMS-ESI *m/z*: [M+Na]⁺ calcd for C₂₀H₃₅NO₃Si, 388.2278; found, 388.2267.



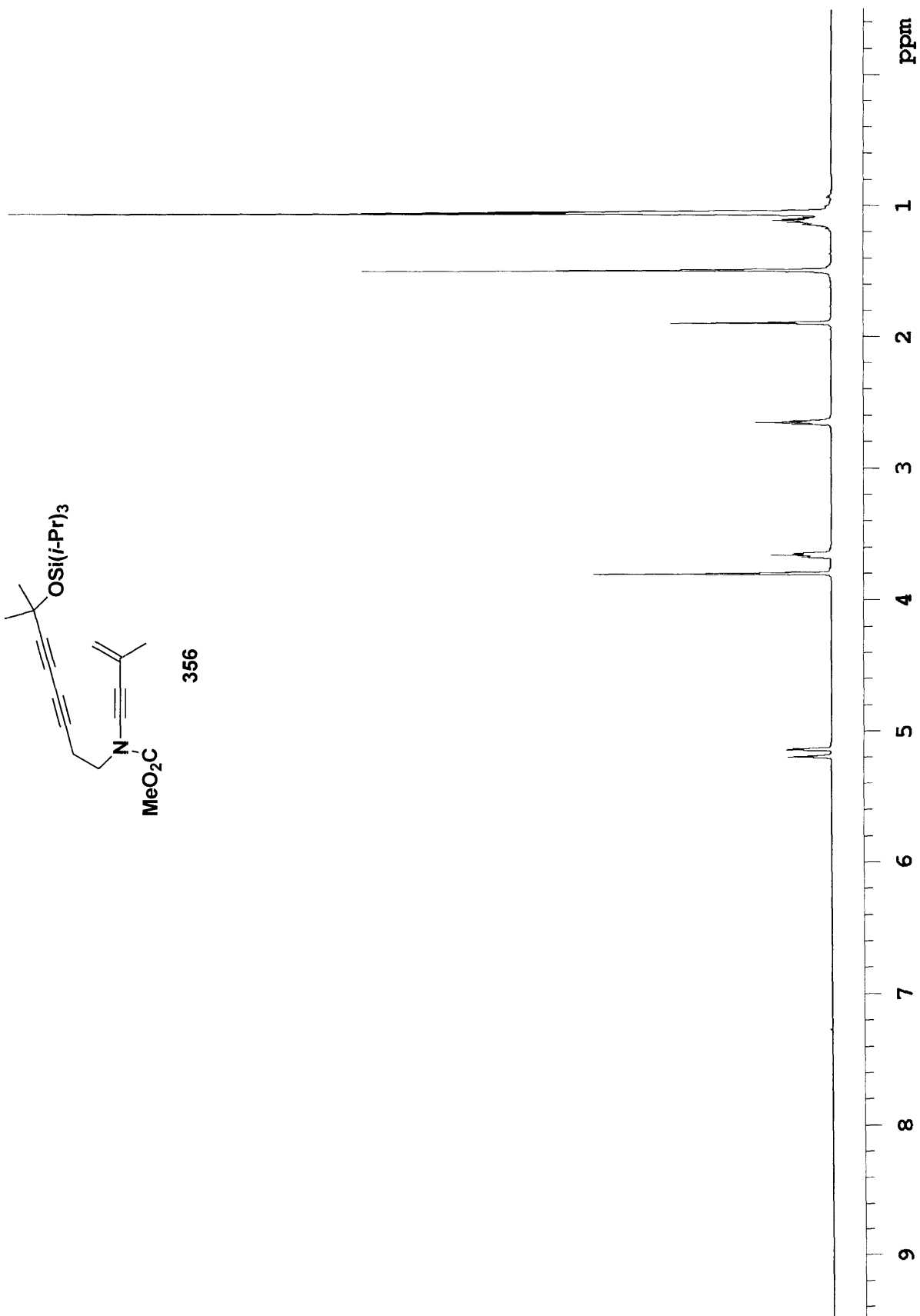


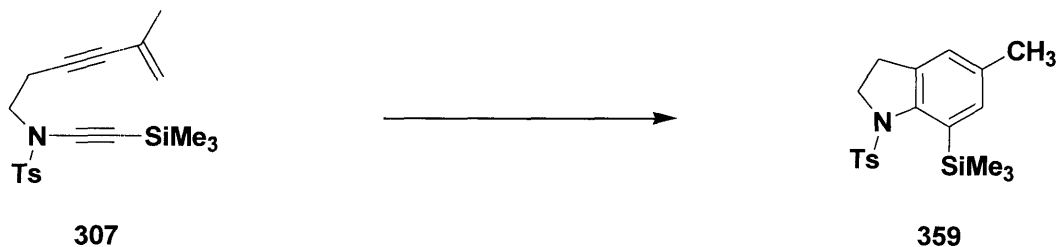
***N*-(Methoxycarbonyl)-*N*-(3-methyl-3-buten-1-ynyl)-7-(triisopropylsiloxy)-7-methyl-octa-3,5-diynylamine (**356**).**

Reaction of a solution of carbamate **355** (0.495 g, 1.35 mmol) in 5.4 mL of pyridine with KHMDS (1.5 mL, 0.90 M in THF, 1.4 mmol), CuI (0.258 g, 1.35 mmol) in 2.7 mL of pyridine, and 1-bromo-3-methyl-3-buten-1-yne (**231**) (4.5 mL, 0.60 M in benzene, 2.7 mmol) according to the general procedure gave 0.599 g of a dark red oil. Column chromatography on 35 g of silica gel (gradient elution with 0–5% EtOAc-hexanes) provided 0.386 g (67%) of ynamide **356** as a pale yellow oil: IR (film) 2944, 2866, 2237, 1736, 1615, and 1446 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.20 (s, 1H), 5.14 (s, 1H), 3.80 (s, 3H), 3.66 (t, $J = 7.3$ Hz, 2H), 2.65 (t, $J = 7.3$ Hz, 2H), 1.90 (s, 3H), 1.50 (s, 6H), 1.12 (sept, $J = 7.0$ Hz, 3H), and 1.06 (d, $J = 7.0$ Hz, 18H); ^{13}C NMR (125 MHz, CDCl_3) δ 155.3, 126.3, 120.0, 81.7, 81.4, 76.6, 72.5, 67.6, 66.6, 66.6, 54.3, 48.7, 33.1, 23.8, 19.0, 18.4, and 13.1; HRMS-ESI m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{39}\text{NO}_3\text{Si}$, 430.2772; found, 430.2779.



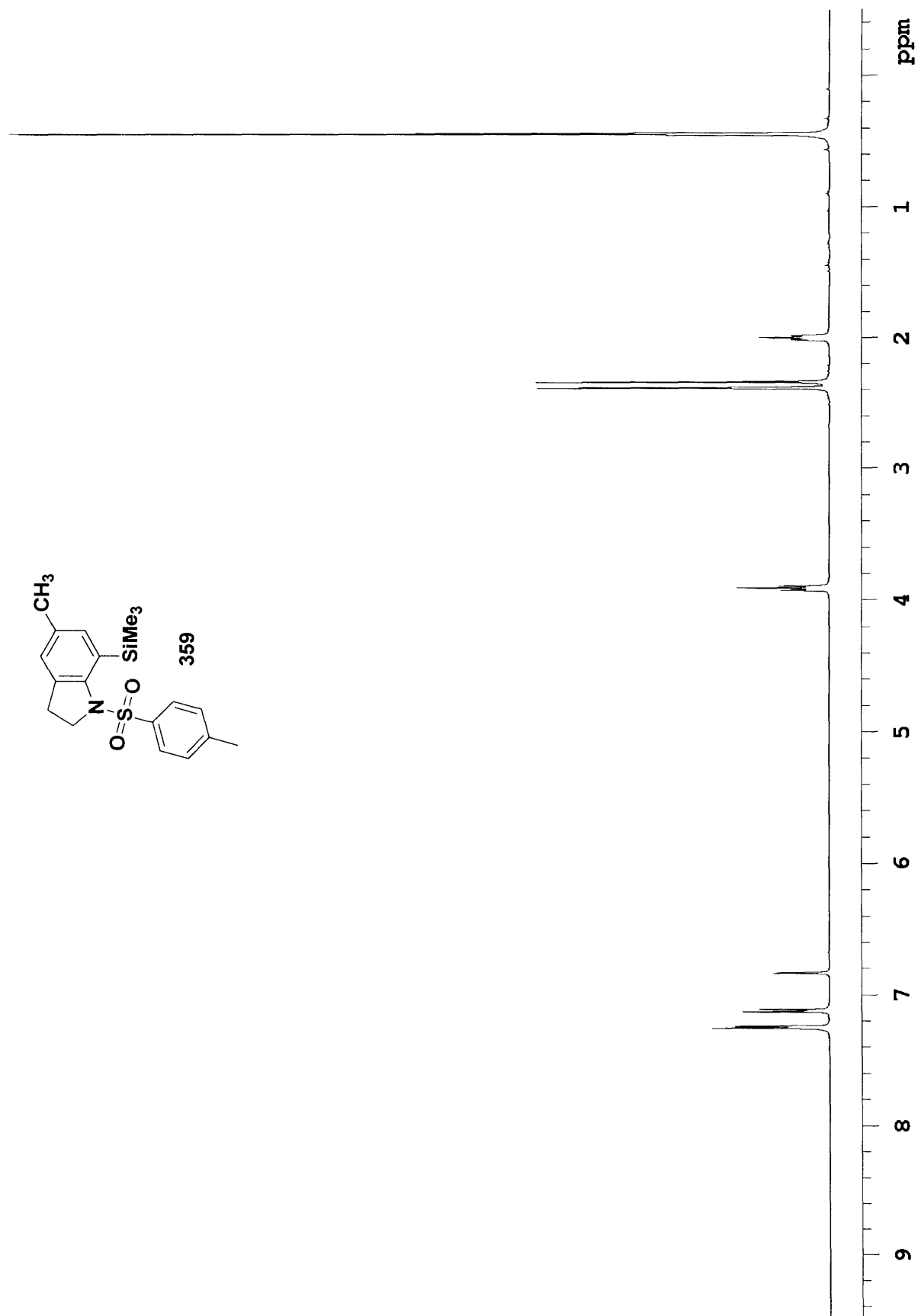
356

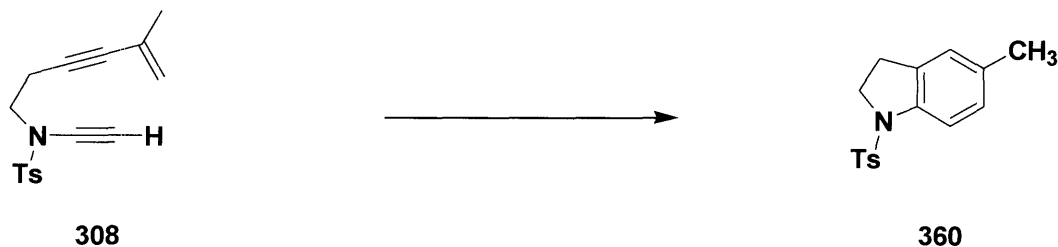




***N*-(*p*-Toluenesulfonyl)-5-methyl-7-(trimethylsilyl)indoline (**359**).**

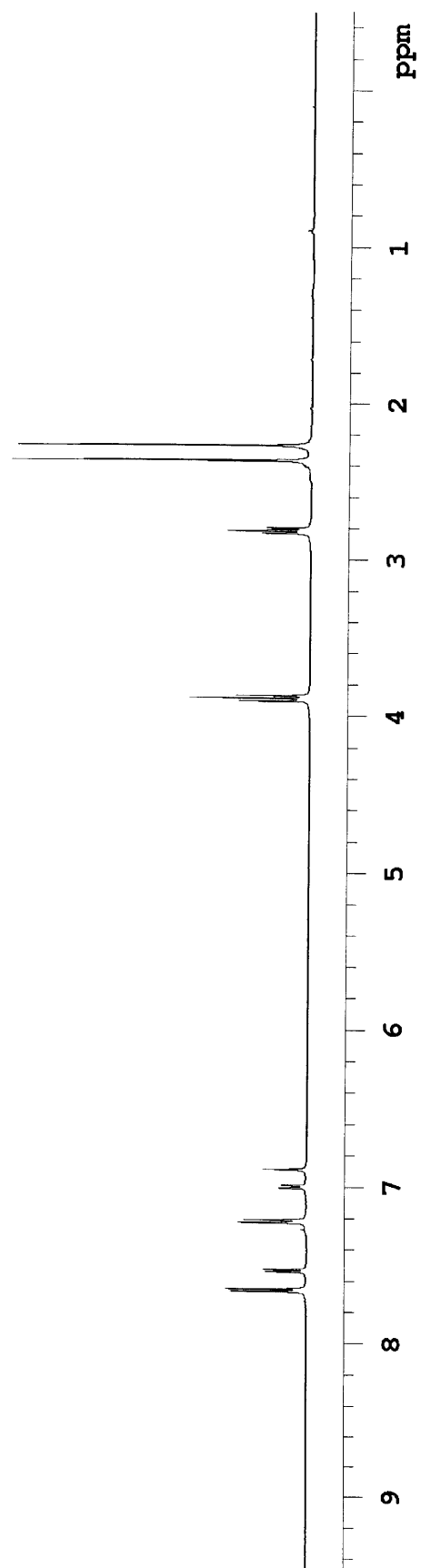
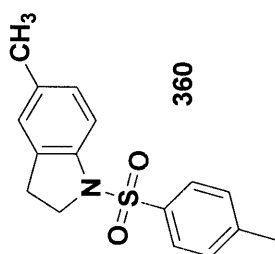
A threaded Pyrex tube (ca. 60 mL capacity) equipped with a rubber septum and argon inlet needle was charged with the ynamide **307** (0.235 g, 0.654 mmol), BHT (0.433 g, 1.96 mmol), and 13 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles, and the tube was then sealed under argon with a threaded Teflon cap. The reaction mixture was heated in an oil bath at 210 °C for 75 min and then allowed to cool to rt. Concentration afforded 0.706 g of a brown oil. Column chromatography on 70 g of silica gel (elution with 2% EtOAc-hexanes) provided 0.131 g (56%) of indoline **359** as a white solid: mp 122–126 °C; IR (CHCl₃) 2955, 1598, 1349, and 1090 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.26 (s, 1H), 7.25 (d, *J* = 7.8 Hz, 2H), 7.12 (d, *J* = 7.8 Hz, 2H), 6.83 (s, 1H), 3.91 (t, *J* = 7.3 Hz, 2H), 2.39 (s, 3H), 2.34 (s, 3H), 2.00 (t, *J* = 7.3 Hz, 2H), and 0.45 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 145.1, 143.9, 136.6, 135.8, 135.4, 134.5, 134.2, 129.4, 127.9, 125.8, 51.6, 28.3, 21.8, 21.4, and 1.1; Anal. Calcd for C₁₉H₂₅NO₂SSi: C, 63.47; H, 7.01; N, 3.90. Found: C, 63.61; H, 7.23; N, 3.86.

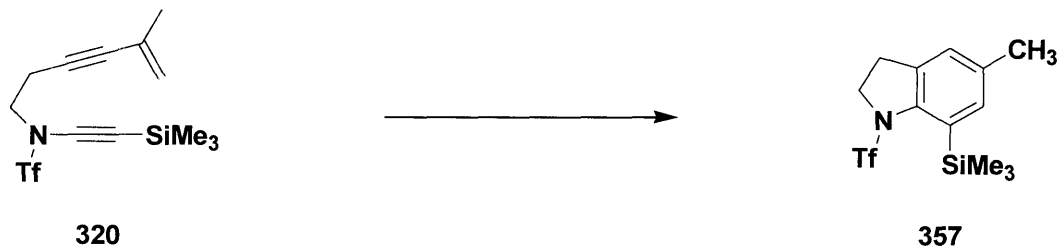




***N*-(*p*-Toluenesulfonyl)-5-methylindoline (**360**).**

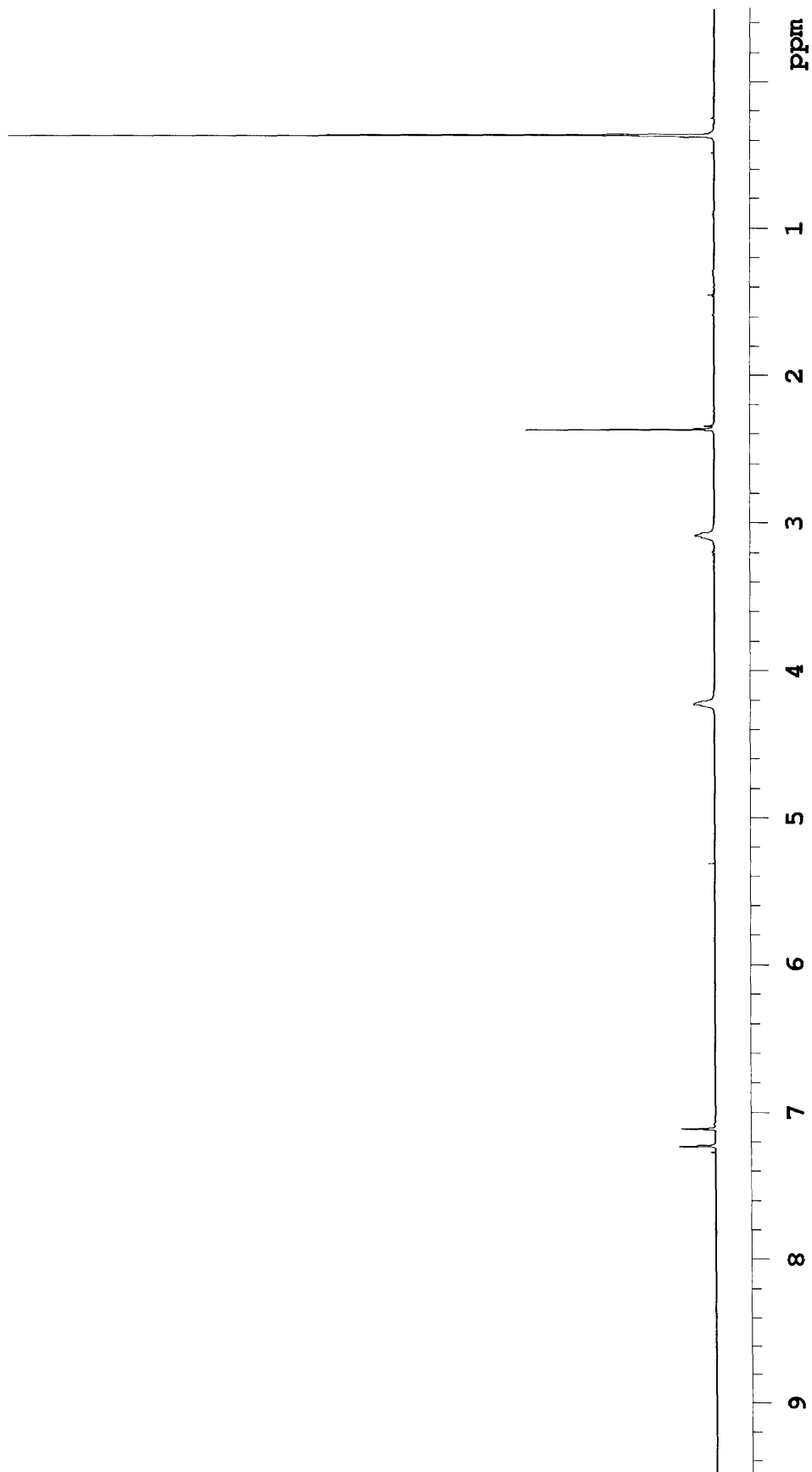
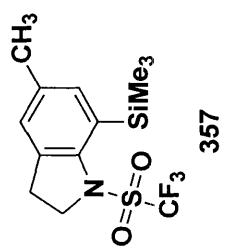
A threaded Pyrex tube (ca. 60 mL capacity) equipped with a rubber septum and argon inlet needle was charged with the ynamide **308** (0.190 g, 0.661 mmol), BHT (0.437 g, 1.98 mmol), and 13 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles, and the tube was then sealed under argon with a threaded Teflon cap. The reaction mixture was heated in an oil bath at 210 °C for 75 min and then allowed to cool to rt. Concentration afforded 0.659 g of a brown oil. Column chromatography on 80 g of silica gel (gradient elution with 2–5% EtOAc-hexanes) provided 0.096 g (51%) of indoline **360** as a white solid: mp 75–77 °C; IR (CH₂Cl₂) 3055, 2924, 1598, 1485, 1353, and 1091 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.66 (d, *J* = 8.2 Hz, 2H), 7.53 (d, *J* = 8.1 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 2H), 7.00 (d, *J* = 8.1 Hz, 1H), 6.89 (s, 1H), 3.89 (t, *J* = 8.4 Hz, 2H), 2.81 (t, *J* = 8.4 Hz, 2H), 2.36 (s, 3H), and 2.27 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 144.1, 139.7, 134.0, 133.6, 132.2, 129.7, 128.3, 127.4, 125.9, 115.1, 50.2, 28.0, 21.7, and 21.0; GC-MS *m/z*: 287 (M⁺).

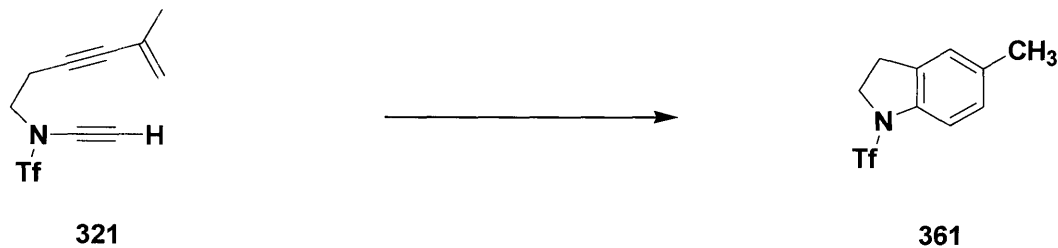




***N*-(Trifluoromethanesulfonyl)-5-methyl-7-(trimethylsilyl)indoline (357).**

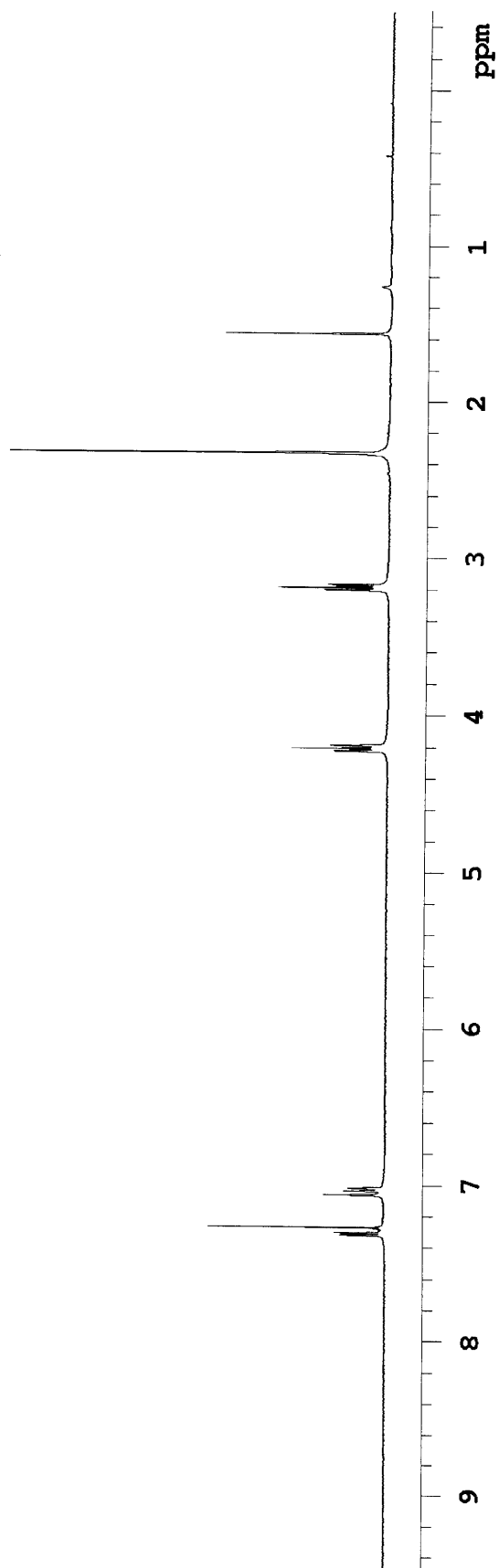
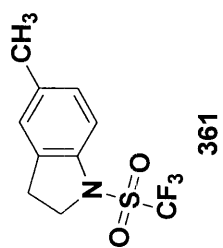
A threaded Pyrex tube (ca. 60 mL capacity) equipped with a rubber septum and argon inlet needle was charged with the ynamide **320** (0.146 g, 0.433 mmol), BHT (0.286 g, 1.30 mmol), and 9 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles, and the tube was then sealed under argon with a threaded Teflon cap. The reaction mixture was heated in an oil bath at 180 °C for 5 h and then allowed to cool to rt. Concentration afforded 0.422 g of a dark brown oil. Column chromatography on 40 g of silica gel (elution with pentanes) provided 0.100 g (68%) of indoline **357** as a white solid: mp 106–109 °C; IR (CHCl₃) 2956, 2865, 1583, 1443, 1396, and 1032 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.23 (s, 1H), 7.11 (s, 1H), 4.22 (app br s, 2H), 3.08 (app br s, 2H), 2.37 (s, 3H), and 0.37 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 142.5, 136.9, 135.9, 135.1, 132.6, 126.5, 120.9 (q, *J*_{CF} = 327 Hz), 53.1, 29.3, 21.3, and 1.0; GC-MS *m/z*: 337 (*M*⁺); Anal. Calcd for C₁₃H₁₈F₃NO₂SSi: C, 46.27; H, 5.38; N, 4.15. Found: C, 46.41; H, 5.51; N, 4.14.

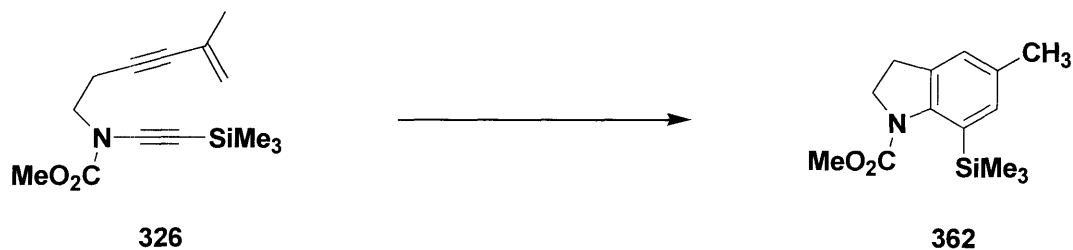




***N*-(Trifluoromethanesulfonyl)-5-methylindoline (**361**).**

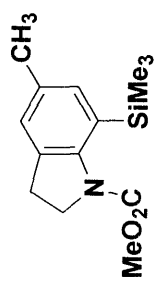
A threaded Pyrex tube (ca. 60 mL capacity) equipped with a rubber septum and argon inlet needle was charged with the ynamide **321** (0.181 g, 0.682 mmol), BHT (0.452 g, 2.05 mmol), and 14 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles, and the tube was then sealed under argon with a threaded Teflon cap. The reaction mixture was heated in an oil bath at 180 °C for 5 h and then allowed to cool to rt. Concentration afforded 0.918 g of a dark brown oil. Column chromatography on 20 g of silica gel (gradient elution with 0.5–1% EtOAc-hexanes) provided 0.102 g (56%) of indoline **361** as a pale yellow oil with spectral characteristics consistent with those previously reported:^{14c} IR (neat) 2926, 2865, 1602, 1488, 1399 and 1059 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.33 (d, *J* = 8.4 Hz, 1H), 7.08 (s, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 4.21 (t, *J* = 8.4 Hz, 2H), 3.19 (t, *J* = 8.4 Hz, 2H), and 2.34 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 137.4, 135.1, 131.5, 128.6, 126.3, 120.5 (q, *J*_{CF} = 324 Hz), 114.3, 51.6, 28.2, and 21.0; GC-MS *m/z*: 265 (M⁺).



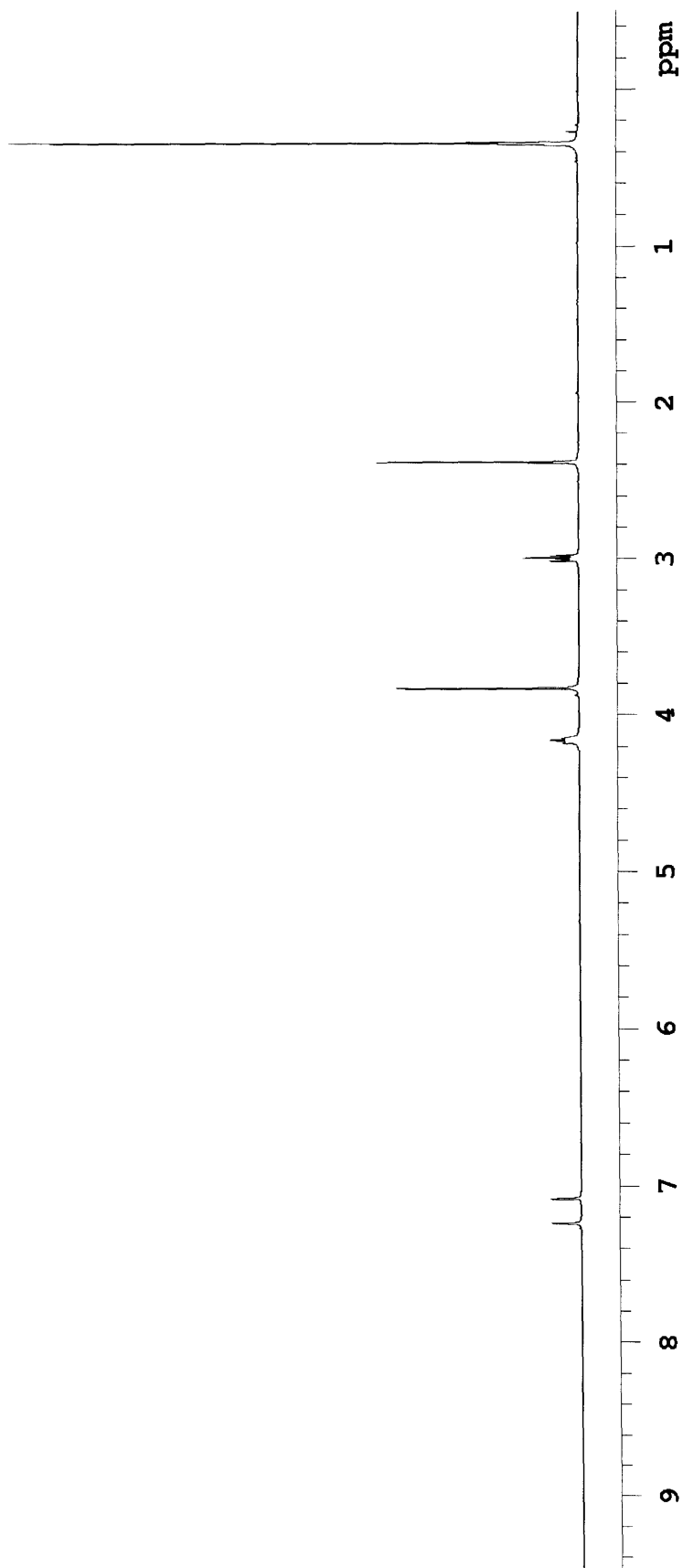


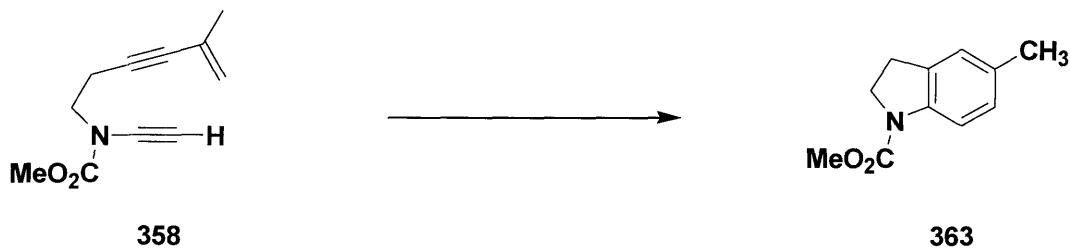
***N*-(Methoxycarbonyl)-5-methyl-7-(trimethylsilyl)indoline (362).**

A threaded Pyrex tube (ca. 60 mL capacity) equipped with a rubber septum and argon inlet needle was charged with the ynamide **326** (0.205 g, 0.778 mmol), BHT (0.171 g, 0.776 mmol), and 16 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles, and the tube was then sealed under argon with a threaded Teflon cap. The reaction mixture was heated in an oil bath at 180 °C for 16 h and then allowed to cool to room temperature. Concentration afforded 0.377 g of a pale brown oil. Column chromatography on 100 g of silica gel (gradient elution with 0–3% EtOAc-hexanes) provided 0.152 g (74%) of indoline **362** as a white solid: mp 65–67 °C; IR (CHCl₃) 3017, 2861, 1720, 1607, 1583, and 1448 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.24 (s, 1H), 7.08 (s, 1H), 4.16 (t, *J* = 7.7 Hz, 2H), 3.83 (s, 3H), 2.99 (t, *J* = 7.7 Hz, 2H), 2.38 (s, 3H), and 0.35 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 155.9, 144.8, 134.5, 133.4, 129.2, 128.6, 126.1, 52.8, 50.0, 29.2, 21.1, and 0.4; GC-MS *m/z*: 263 (M⁺); Anal. Calcd for C₁₄H₂₁NO₂Si: C, 63.84; H, 8.04; N, 5.32. Found: C, 64.10; H, 7.90; N, 5.40.



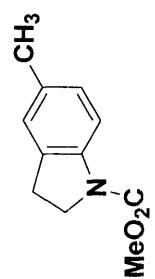
362



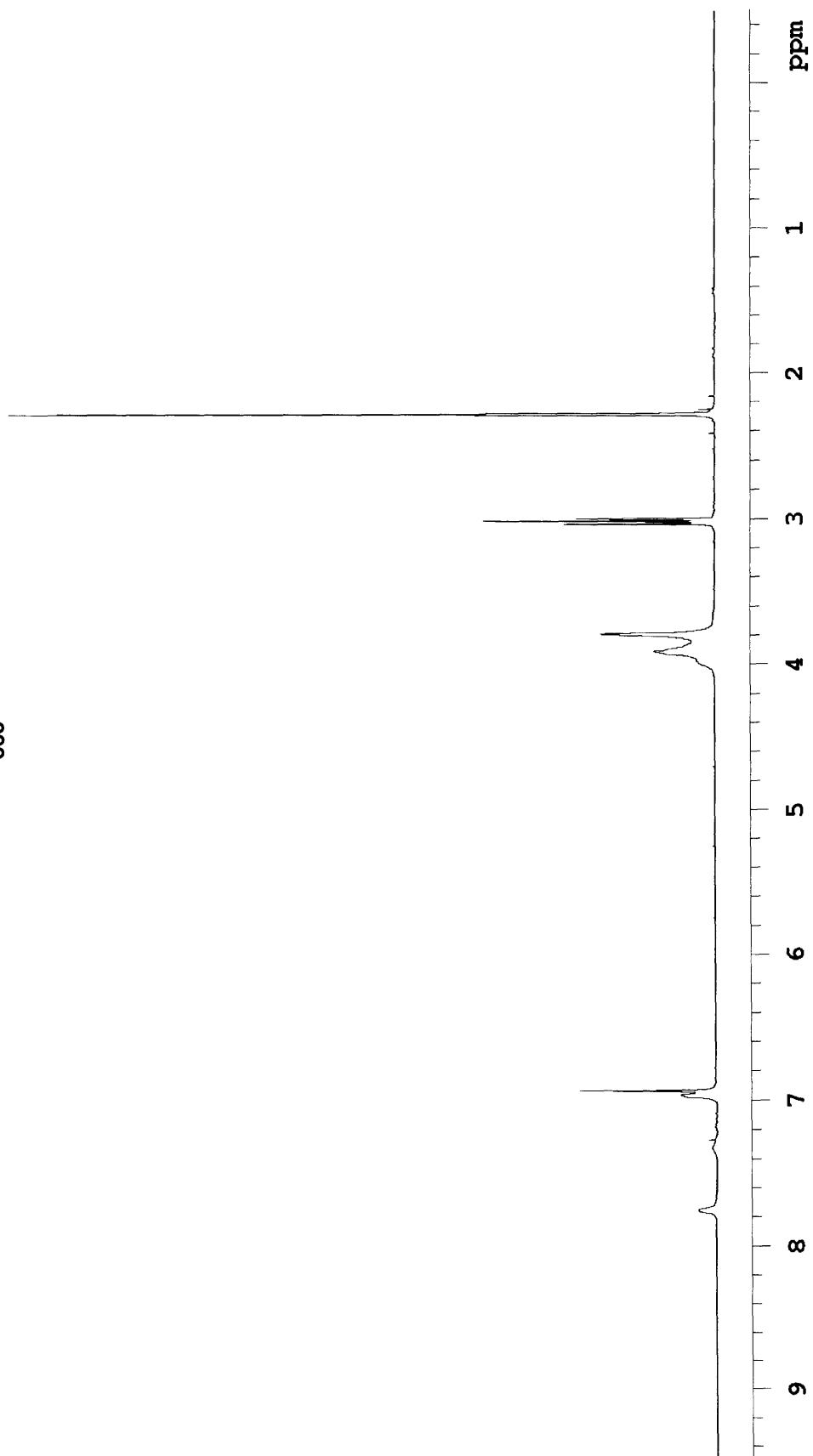


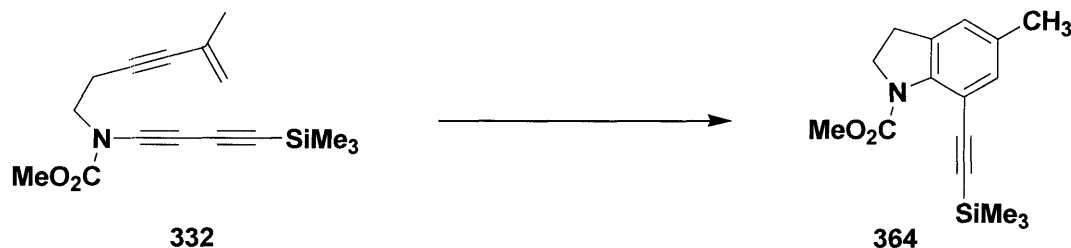
***N*-(Methoxycarbonyl)-5-methylindoline (363).**

A threaded Pyrex tube (ca. 60 mL capacity) equipped with a rubber septum and argon inlet needle was charged with the ynamide **358** (0.190 g, 0.994 mmol), BHT (0.219 g, 0.994 mmol), and 20 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles, and the tube was then sealed under argon with a threaded Teflon cap. The reaction mixture was heated in an oil bath at 210 °C for 2 h and then allowed to cool to rt. Concentration afforded 0.414 g of a pale brown oil. Column chromatography on 100 g of silica gel (gradient elution with 0–3% EtOAc-hexanes) provided 0.134 g (71%) of indoline **363** as a pale yellow solid: mp 55–58 °C; IR (film) 2952, 2919, 1710, 1613, 1498, and 1450 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.76 (br s, 1H), 6.97 (br s, 1H), 6.94 (s, 1H), 3.91 (br s, 2H), 3.79 (br s, 3H), 3.02 (t, *J* = 8.7 Hz, 2H), and 2.29 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 153.4, 140.2, 131.9, 130.8, 127.7, 125.2, 114.2, 52.2, 47.2, 27.4, and 20.8; Anal. Calcd for C₁₁H₁₃NO₂: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.34; H, 7.13; N, 7.02.



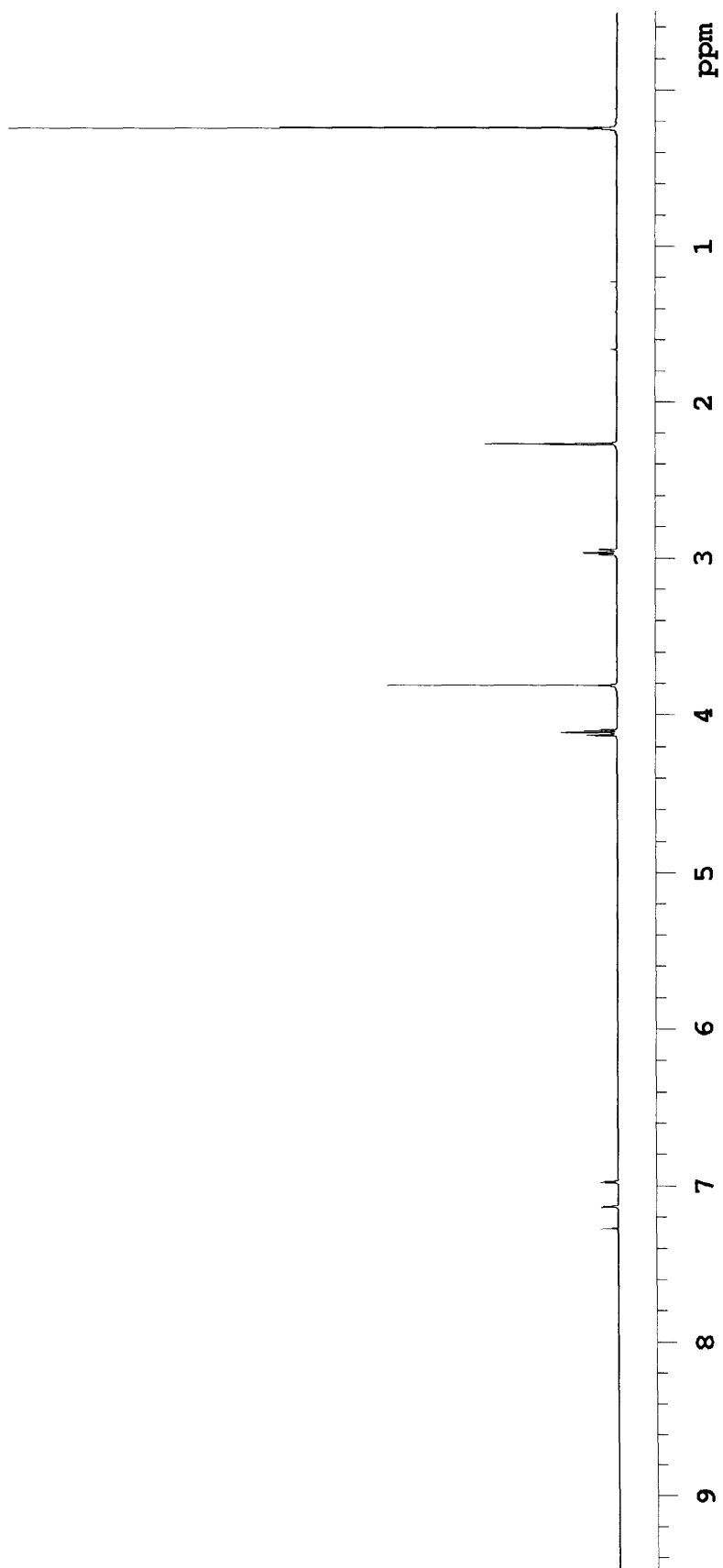
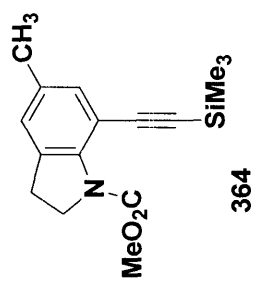
363

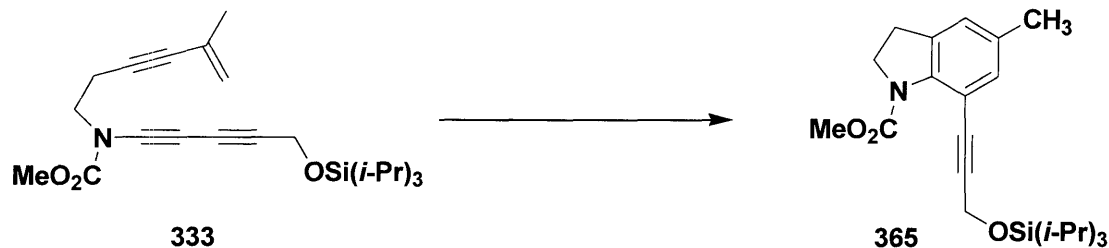




***N*-(Methoxycarbonyl)-5-methyl-7-[2-(trimethylsilyl)ethynyl]indoline (364).**

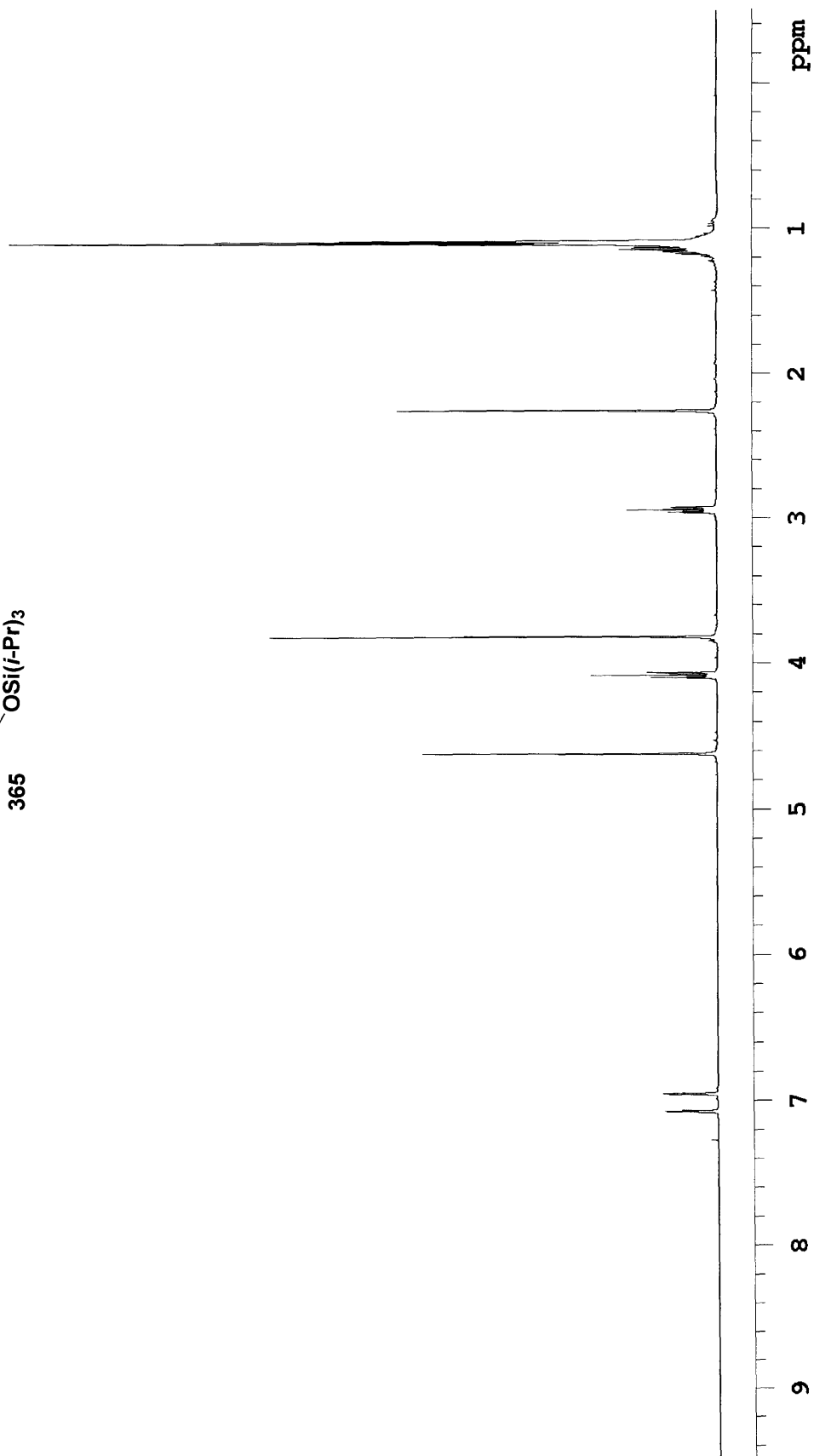
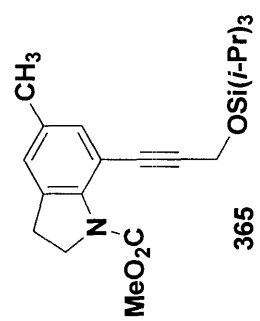
A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and reflux condenser fitted with an argon inlet adapter was charged with ynamide **332** (0.182 g, 0.633 mmol), BHT (0.140 g, 0.635 mmol), and 13 mL of toluene. The septum was replaced with a glass stopper and the solution was heated at reflux for 14 h. The reaction mixture was allowed to cool to room temperature and then concentrated to afford 0.336 g of a dark brown oil. Column chromatography on 100 g of silica gel (gradient elution with 0–5% EtOAc-hexanes) provided 0.125 g (69%) of indoline **364** as a white solid: mp 77–81 °C; IR (CH₂Cl₂) 2957, 2151, 1708, 1588, and 1443 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.13 (s, 1H), 6.97 (s, 1H), 4.11 (t, *J* = 7.9 Hz, 2H), 3.81 (s, 3H), 2.96 (t, *J* = 7.9 Hz, 2H), 2.26 (s, 3H), and 0.24 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 154.7, 140.8, 134.7, 133.5, 132.8, 126.2, 112.4, 103.0, 98.2, 52.4, 50.6, 29.0, 20.7, and 0.2; Anal. Calcd for C₁₆H₂₁NO₂Si: C, 66.86; H, 7.36; N, 4.87. Found: C, 66.43; H, 7.63; N, 4.56.

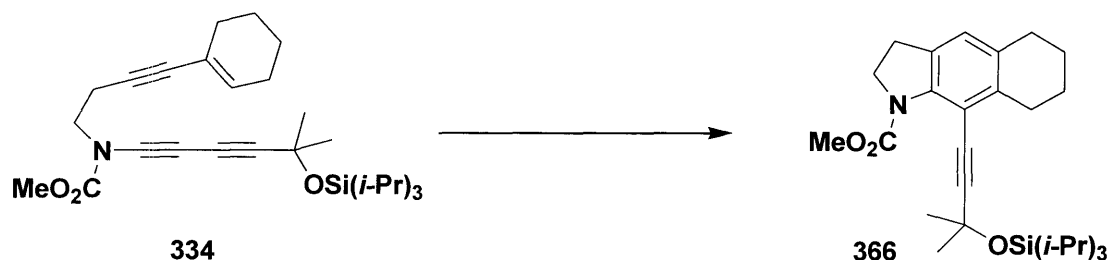




***N*-(Methoxycarbonyl)-5-methyl-7-[3-(triisopropylsiloxy)-1-propynyl]indoline (365).**

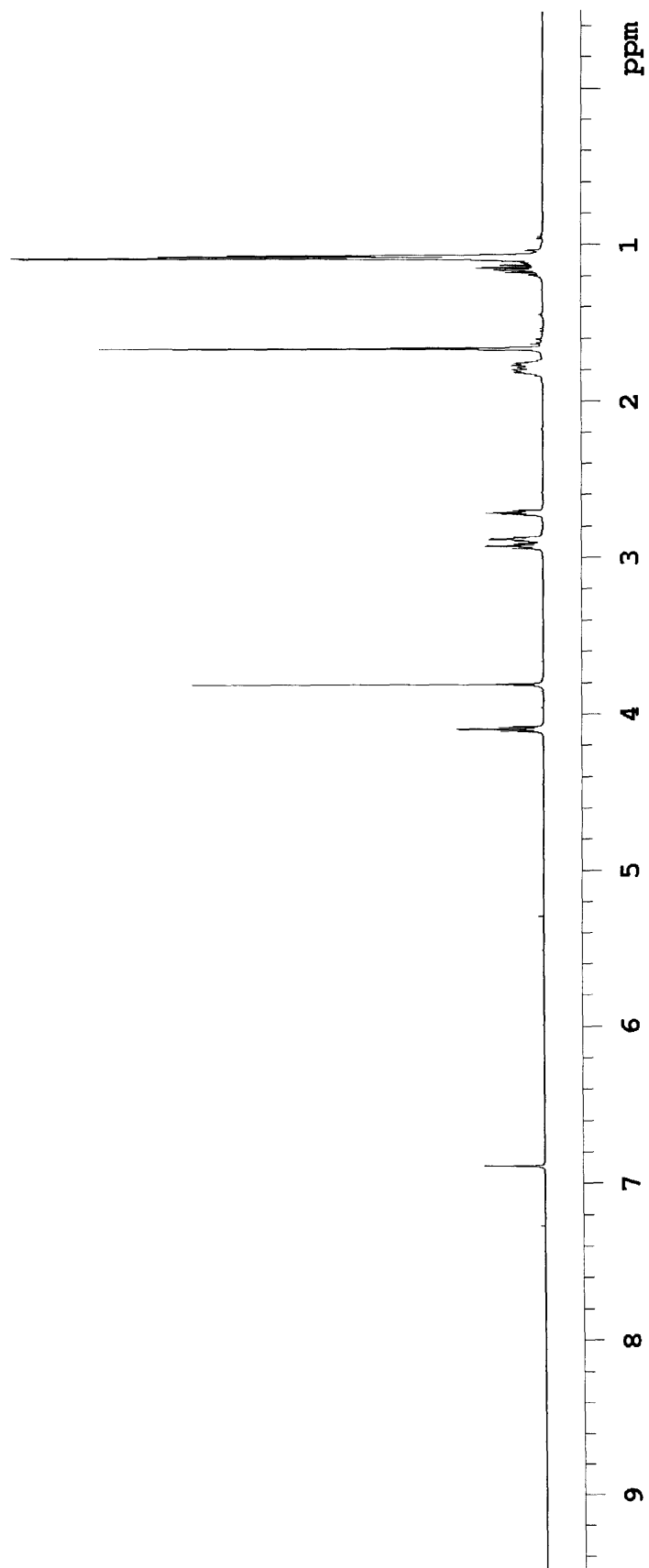
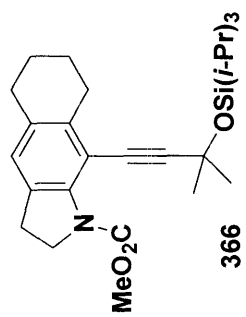
A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and reflux condenser fitted with an argon inlet adapter was charged with ynamide **333** (0.287 g, 0.715 mmol), BHT (0.158 g, 0.717 mmol), and 14 mL of toluene. The septum was replaced with a glass stopper and the solution was heated at reflux for 14 h. The reaction mixture was allowed to cool to room temperature and then concentrated to afford 0.450 g of a red oil. Column chromatography on 100 g of silica gel (gradient elution with 0–15% EtOAc-hexanes) provided 0.123 g (43%) of indoline **365** as a beige solid: mp 53–55 °C; IR (CH₂Cl₂) 2944, 2865, 2235, 1708, 1592, and 1443 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.07 (s, 1H), 6.95 (s, 1H), 4.62 (s, 2H), 4.08 (t, *J* = 7.9 Hz, 2H), 3.82 (s, 3H), 2.94 (t, *J* = 7.9 Hz, 2H), 2.26 (s, 3H), 1.14 (sept, *J* = 6.1 Hz, 3H), and 1.10 (d, *J* = 6.1 Hz, 18H); ¹³C NMR (125 MHz, CDCl₃) δ 154.7, 140.8, 134.7, 133.5, 132.4, 125.8, 112.4, 92.1, 82.5, 52.7, 52.5, 50.6, 29.0, 20.8, 18.1, and 12.1; Anal. Calcd for C₂₃H₃₅NO₃Si: C, 68.78; H, 8.78; N, 3.49. Found: C, 69.02; H, 9.05; N, 3.40.

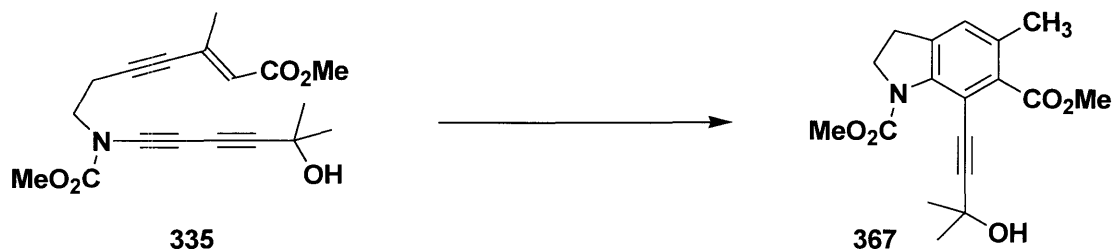




***N*-(Methoxycarbonyl)-9-[3-(triisopropylsiloxy)-3-methyl-1-butynyl]-5,6,7,8-tetrahydrobenzo[*f*]indoline (366).**

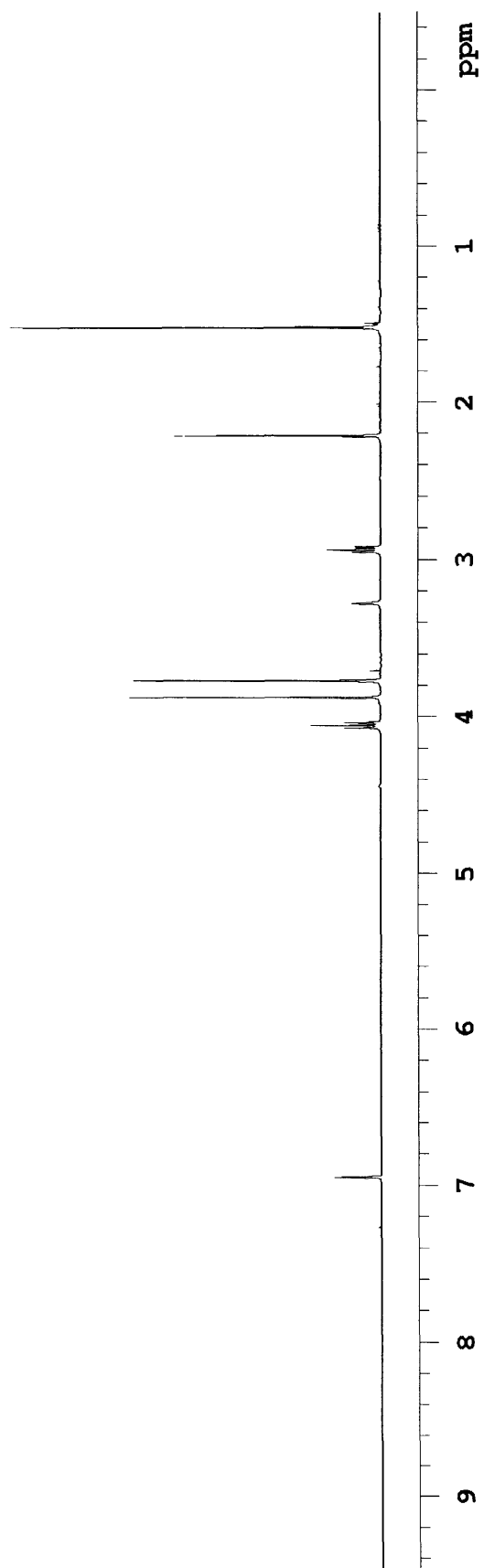
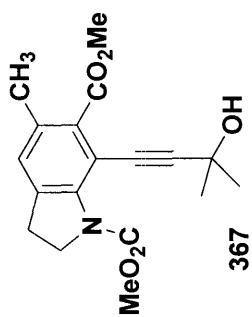
A 25-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with ynamide **334** (0.216 g, 0.460 mmol), BHT (0.101 g, 0.458 mmol), and 9 mL of toluene. The reaction mixture was heated at reflux for 8 h and then allowed to cool to room temperature and concentrated to afford 0.322 g of a pale brown oil. Column chromatography on 60 g of silica gel (gradient elution with 0–5% EtOAc-hexanes) provided 0.165 g (76%) of indoline **366** as a pale yellow oil: IR (neat) 2941, 2864, 2219, 1709, 1606, and 1440 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.89 (s, 1H), 4.09 (t, $J = 7.6$ Hz, 2H), 3.81 (s, 3H), 2.92 (t, $J = 7.6$ Hz, 2H), 2.88 (app t, $J = 6.1$ Hz, 2H), 2.71 (app t, $J = 6.1$ Hz, 2H), 1.74–1.84 (m, 4H), 1.67 (s, 6H), 1.15 (sept, $J = 7.0$ Hz, 3H), and 1.08 (d, $J = 7.0$ Hz, 18H); ^{13}C NMR (125 MHz, CDCl_3) δ 154.8, 142.1, 138.4, 133.3, 131.6, 125.2, 113.2, 104.2, 78.7, 67.2, 52.8, 51.2, 33.6, 29.9, 29.2, 28.5, 23.3, 23.0, 18.5, and 13.2; Anal. Calcd for $\text{C}_{28}\text{H}_{43}\text{NO}_3\text{Si}$: C, 71.59; H, 9.23; N, 2.98. Found: C, 71.32; H, 9.42; N, 3.02.

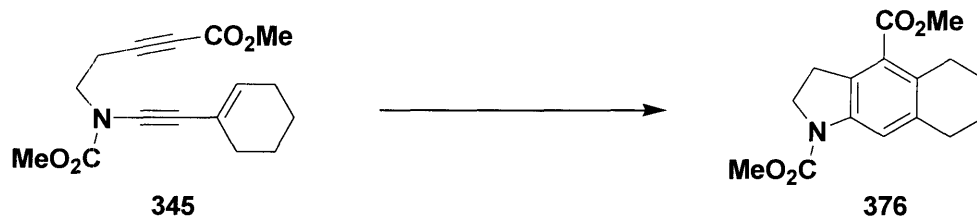




***N*-(Methoxycarbonyl)-7-(3-hydroxy-3-methyl-1-butynyl)-6-methoxycarbonyl-5-methylindoline (367).**

A 50-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with ynamide **335** (0.316 g, 0.954 mmol), BHT (0.210 g, 0.953 mmol), and 19 mL of toluene. The reaction mixture was heated at reflux for 5 h and then allowed to cool to room temperature and concentrated to afford 0.553 g of a brown oil. Column chromatography on 80 g of silica gel (gradient elution with 30–45% EtOAc-hexanes) provided 0.125 g (40%) of indoline **367** as a pale yellow solid: mp 118–120 °C; IR (film) 3451, 2981, 2954, 2226, 1727, 1710, 1601, 1584, and 1442 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.95 (s, 1H), 4.05 (t, *J* = 7.9 Hz, 2H), 3.88 (s, 3H), 3.77 (s, 3H), 3.28 (s, 1H), 2.93 (t, *J* = 7.9 Hz, 2H), 2.21 (s, 3H), and 1.52 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 169.3, 154.3, 141.4, 136.2, 135.9, 130.9, 126.5, 110.0, 102.6, 77.6, 65.4, 52.9, 52.4, 50.6, 31.3, 28.9, and 19.2; HRMS-ESI *m/z*: [M+Na]⁺ calcd for C₁₈H₂₁NO₅, 354.1312; found, 354.1296.

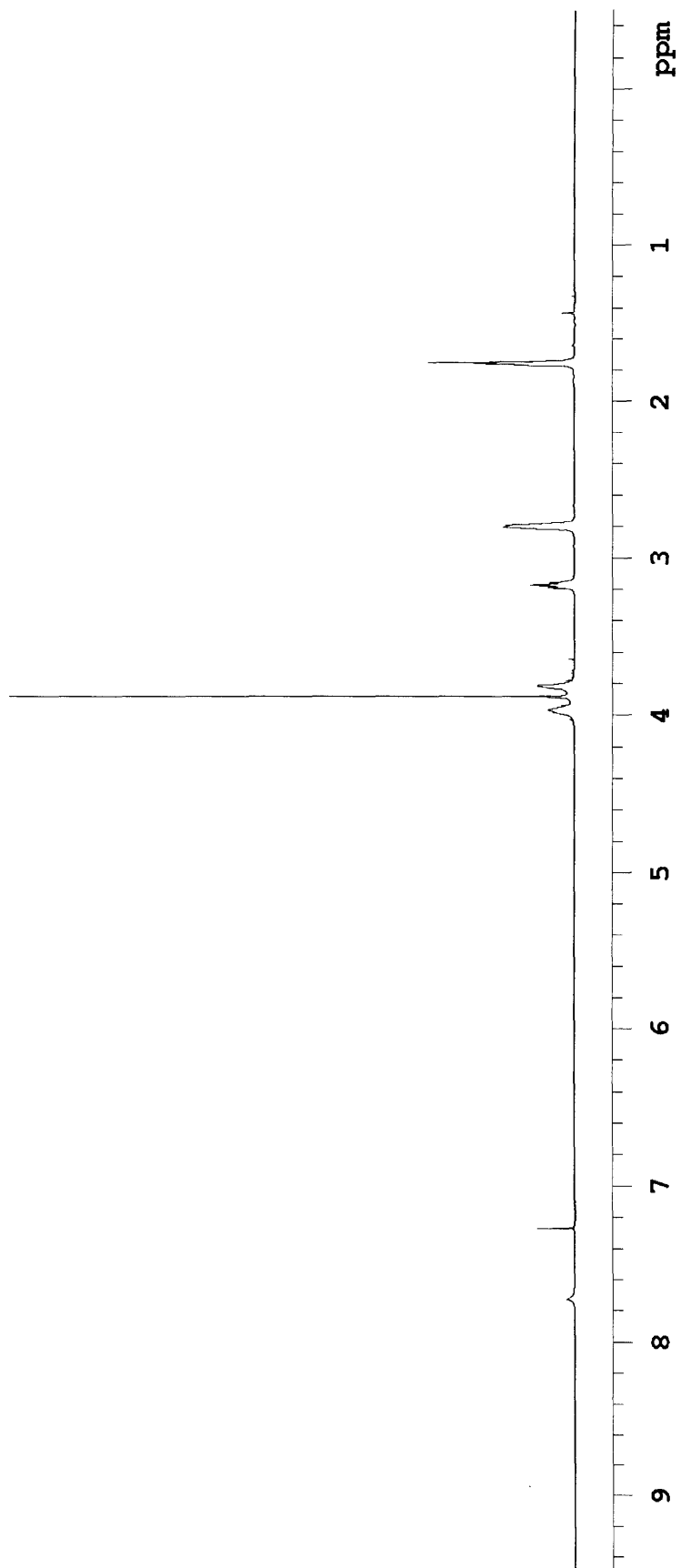
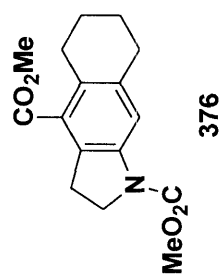


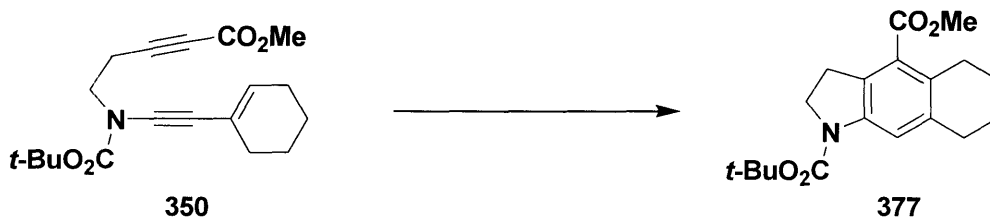


***N*-(Methoxycarbonyl)-4-methoxycarbonyl-5,6,7,8-tetrahydrobenzo[*f*]indoline (376).**

Thermal Cycloaddition. A 50-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with ynamide **345** (0.325 g, 1.12 mmol), BHT (0.249 g, 1.13 mmol), and 23 mL of toluene. The reaction mixture was heated at reflux for 8 h and then allowed to cool to room temperature and concentrated to afford 0.581 g of a pale yellow solid. Column chromatography on 80 g of silica gel (gradient elution with 5–15% EtOAc-hexanes) provided 0.312 g (96%) of indoline **376** as an off-white solid.

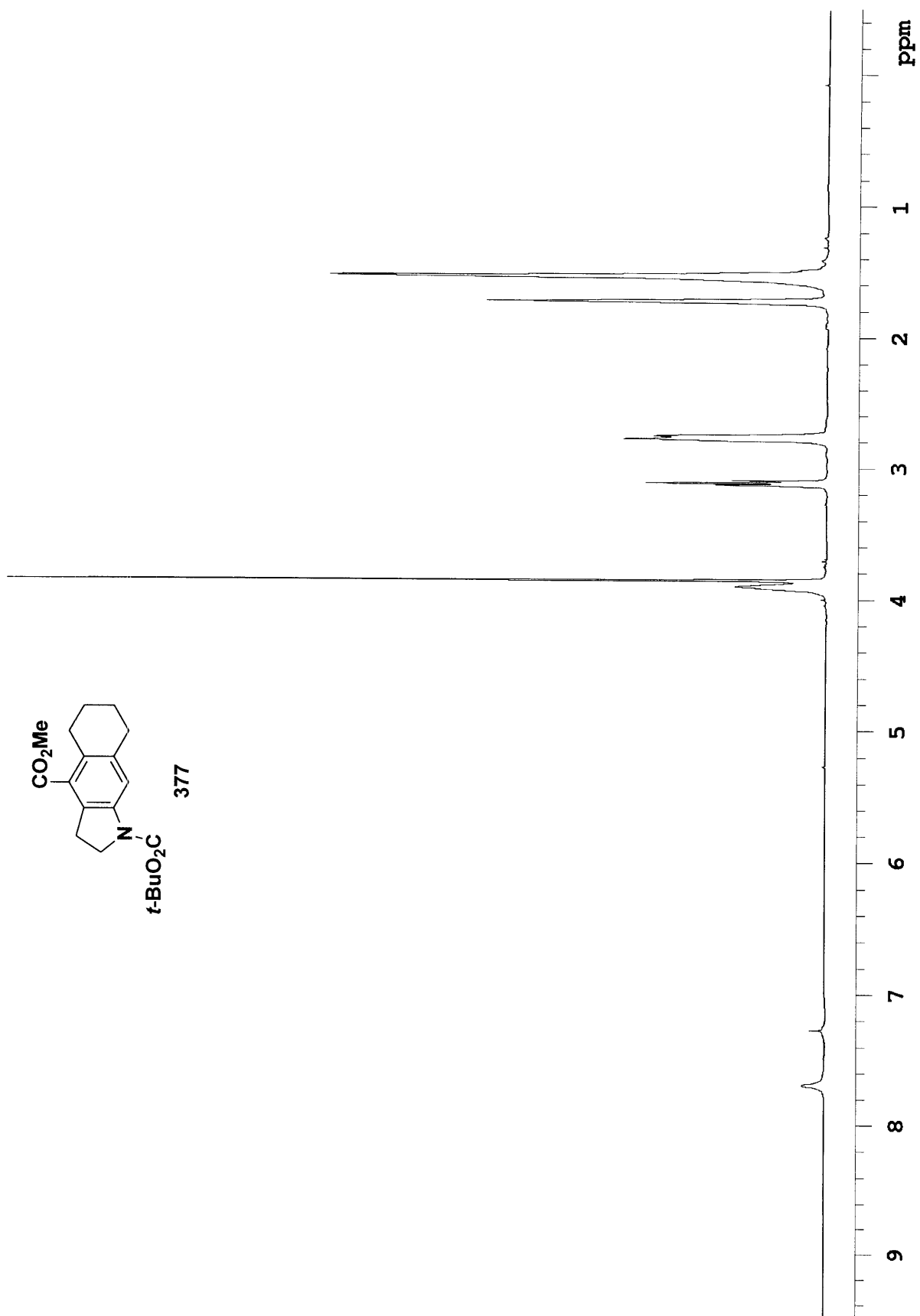
Lewis Acid-Promoted Cycloaddition. A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with ynamide **345** (0.101 g, 0.349 mmol) and 7 mL of CH₂Cl₂ and cooled at 0 °C while 0.87 mL of Me₂AlCl solution (1.0 M in hexanes, 0.87 mmol) was added via syringe over 1 min. The resulting pale orange solution was stirred at 0 °C for 1 h, and then the ice bath was removed and the solution was stirred at rt for 2 h. The reaction mixture was diluted with 70 mL of Et₂O, 20 mL of satd NaHCO₃ solution, and 30 mL of water. The aqueous layer was separated and extracted with three 25-mL portions of Et₂O, and the combined organic layers were washed with 50 mL of satd NaCl solution, dried over MgSO₄, filtered, and concentrated to afford 0.108 g of a yellow oil. Two successive purifications by column chromatography on 20 g of silica gel (gradient elution with 5–20% EtOAc-hexanes) provided 0.078 g (78%) of indoline **376** as an off-white solid: mp 108–110 °C; IR (film) 2931, 1721, 1712, 1603, 1469, and 1441 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.73 (br s, 1H), 3.97 (br s, 2H), 3.88 (s, 3H), 3.82 (br s, 3H), 3.17 (t, *J* = 8.4 Hz, 2H), 2.80 (m, 4H), and 1.76 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 168.5, 153.3, 140.4, 137.4, 130.0, 128.7, 128.3, 117.3, 52.3, 51.5, 47.2, 30.4, 27.6, 27.2, 23.1, and 22.6; HRMS-ESI *m/z*: [M+H]⁺ calcd for C₁₆H₁₉NO₄, 290.1387; found, 290.1379.

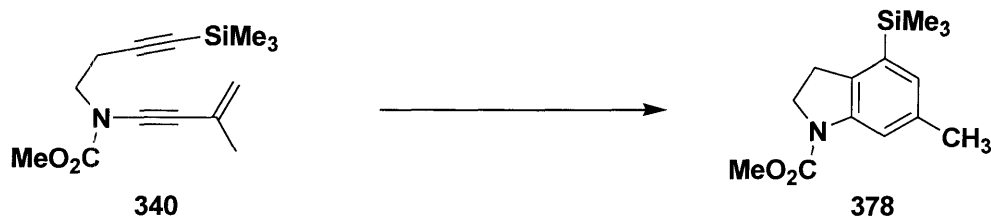




***N*-(tert-Butoxycarbonyl)-4-methoxycarbonyl-5,6,7,8-tetrahydrobenzo[*f*]indoline (377).**

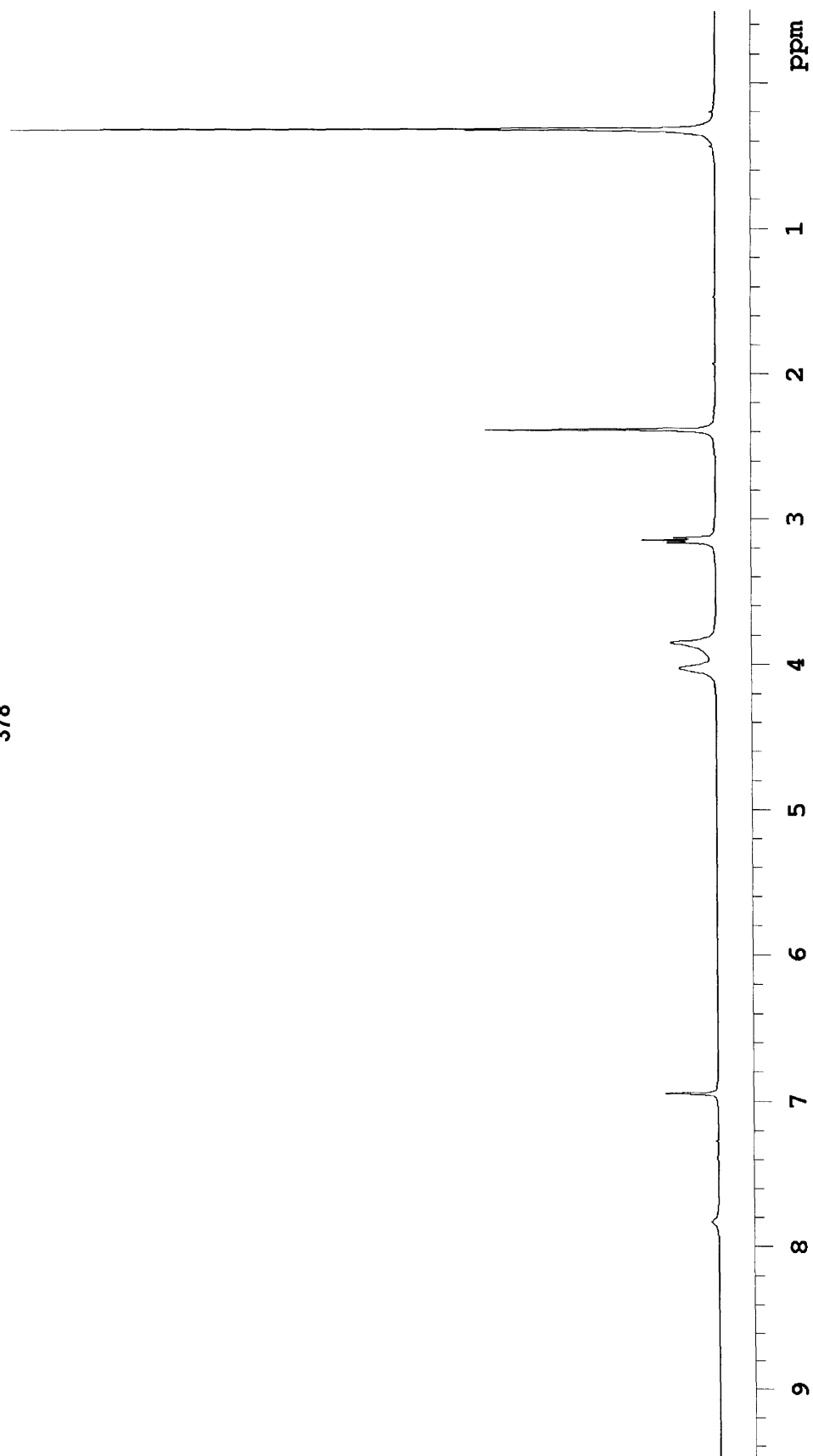
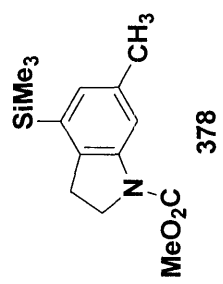
A 50-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with ynamide **350** (0.212 g, 0.640 mmol), BHT (0.141 g, 0.640 mmol), and 13 mL of toluene. The reaction mixture was heated at reflux for 8 h and then allowed to cool to room temperature and concentrated to afford 0.347 g of a yellow oil. Column chromatography on 80 g of silica gel (gradient elution with 0–2% EtOAc-hexanes) provided 0.192 g (91%) of indoline **377** as a white solid: mp 78–81 °C; IR (film) 2932, 1723, 1704, 1603, and 1468 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.69 (br s, 1H), 3.90 (br s, 2H), 3.85 (s, 3H), 3.11 (t, *J* = 8.4 Hz, 2H), 2.76 (m, 4H), 1.73 (m, 4H), and 1.53 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 168.9, 152.6, 140.8, 137.5, 129.7, 128.9, 128.5, 117.6, 80.5, 51.7, 47.7, 30.6, 28.5, 27.6, 27.3, 23.3, and 22.8; HRMS-ESI *m/z*: [M+Na]⁺ calcd for C₁₉H₂₅NO₄, 354.1676; found, 354.1683.

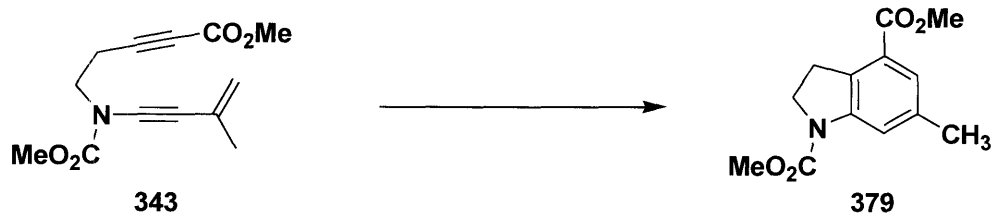




***N*-(Methoxycarbonyl)-6-methyl-4-(trimethylsilyl)indoline (378).**

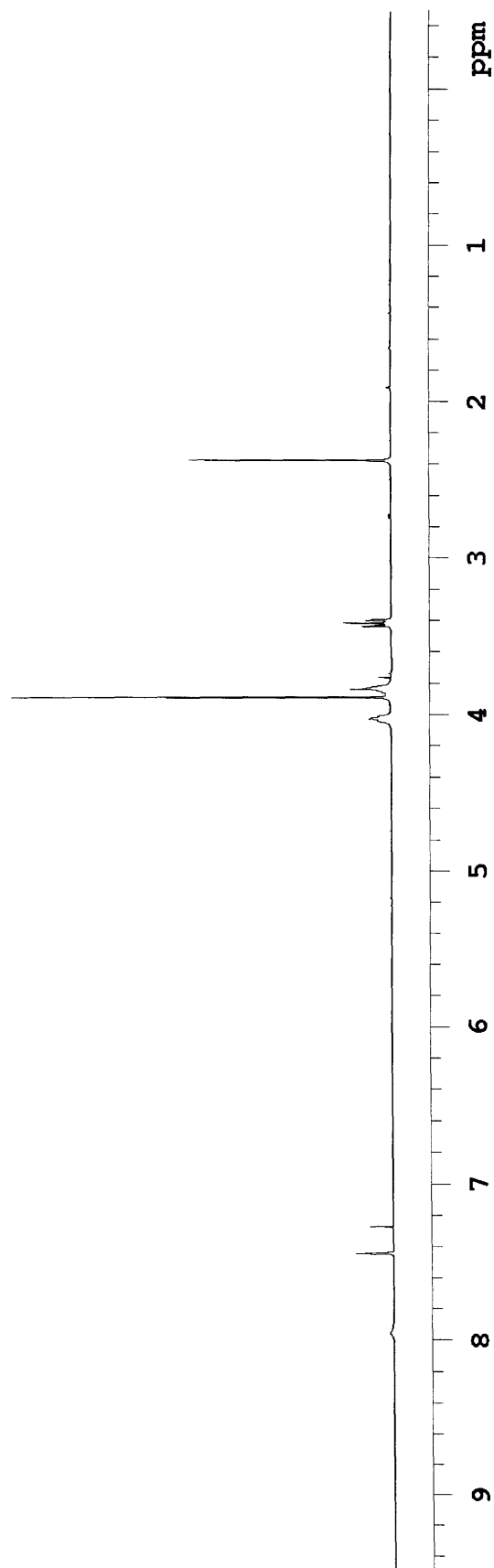
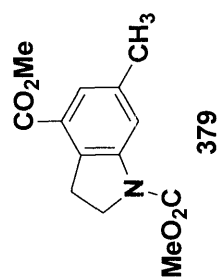
A threaded Pyrex tube (ca. 60 mL capacity) equipped with a rubber septum and argon inlet needle was charged with the ynamide **340** (0.180 g, 0.683 mmol), BHT (0.151 g, 0.685 mmol), and 14 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles, and the tube was then sealed under argon with a threaded Teflon cap. The reaction mixture was heated in an oil bath at 180 °C for 16 h and then allowed to cool to room temperature. Concentration afforded 0.334 g of a pale brown oil. Column chromatography on 100 g of silica gel (gradient elution with 0–2% EtOAc-hexanes) provided 0.155 g (86%) of indoline **378** as a white solid: mp 89–91 °C; IR (film) 2954, 1716, 1596, 1569, 1450, and 1420 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.83 (br s, 1H), 6.94 (s, 1H), 4.02 (br s, 2H), 3.85 (br s, 3H), 3.14 (t, *J* = 8.5 Hz, 2H), 2.38 (s, 3H), and 0.32 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 153.8, 142.2, 136.7, 135.4, 133.1, 128.8, 116.5, 52.5, 47.6, 28.4, 21.8, and -0.7; Anal. Calcd for C₁₄H₂₁NO₂Si: C, 63.84; H, 8.04; N, 5.32. Found: C, 63.82; H, 8.16; N, 5.24.

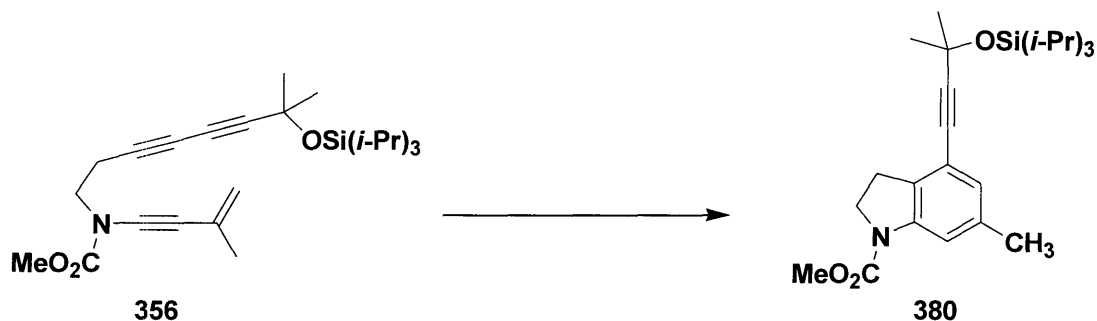




***N*-(Methoxycarbonyl)-4-(methoxycarbonyl)-6-methylindoline (379).**

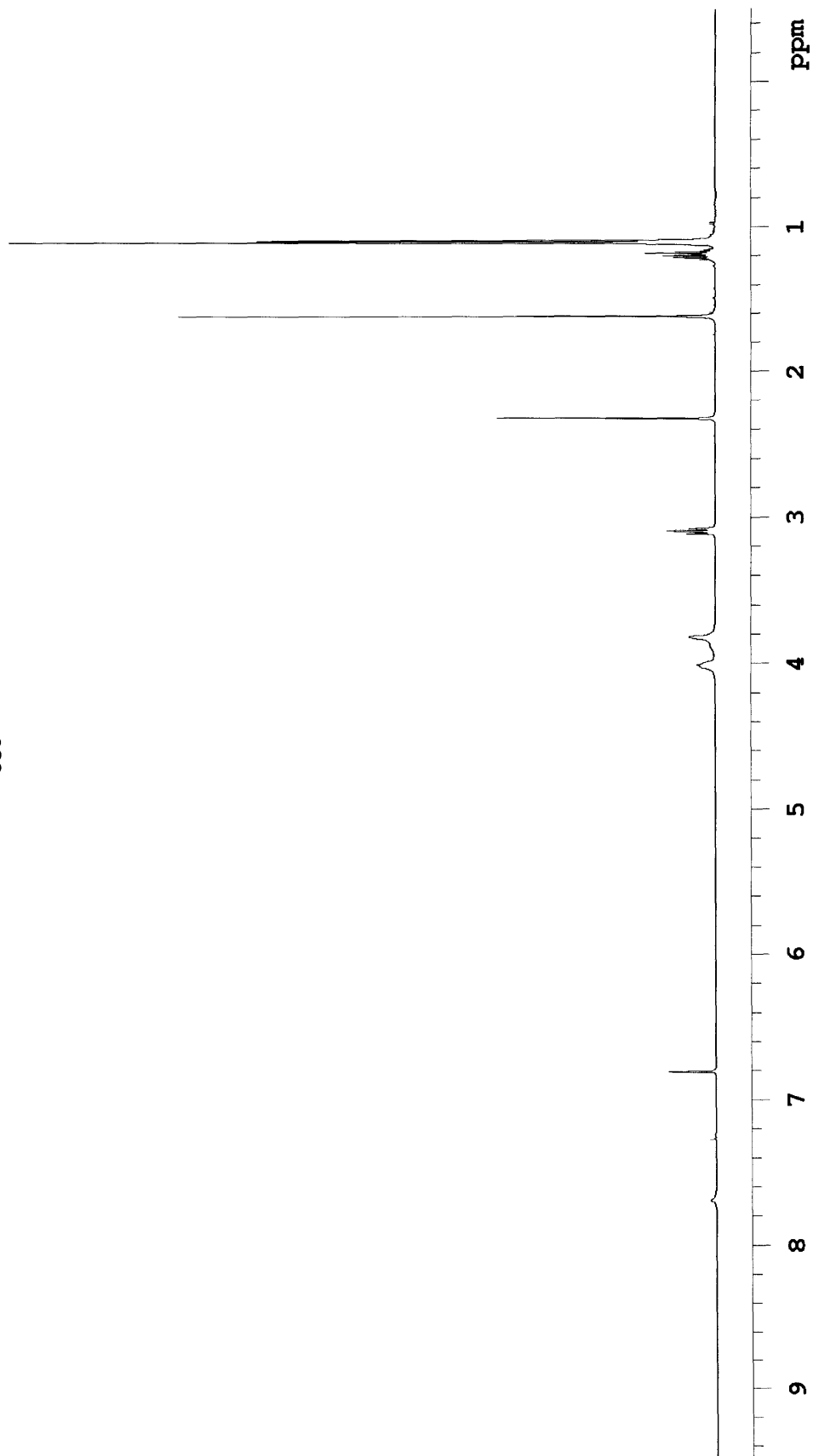
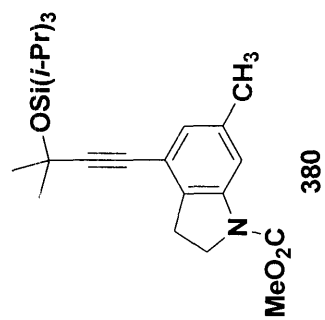
A 25-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with ynamide **343** (0.132 g, 0.530 mmol), BHT (0.117 g, 0.531 mmol), and 11 mL of toluene. The reaction mixture was heated at reflux for 30 h and then allowed to cool to room temperature and concentrated to afford 0.252 g of a pale red solid. Column chromatography on 40 g of silica gel (gradient elution with 5–10% EtOAc-hexanes) provided 0.126 g (95%) of indoline **379** as a white solid: mp 102–105 °C; IR (film) 2957, 1724, 1712, 1609, 1487, and 1443 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.95 (br s, 1H), 7.44 (s, 1H), 4.02 (t, *J* = 8.5 Hz, 2H), 3.89 (s, 3H), 3.83 (br s, 3H), 3.42 (t, *J* = 8.5 Hz, 2H), and 2.37 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 166.9, 153.7, 143.9, 137.8, 131.2, 126.0, 124.4, 119.4, 52.6, 51.8, 47.9, 28.5, and 21.6; HRMS-ESI *m/z*: [M+H]⁺ calcd for C₁₃H₁₅NO₄, 250.1074; found, 250.1071.

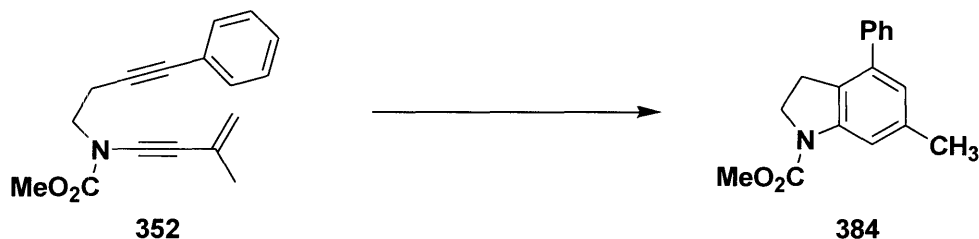




***N*-(Methoxycarbonyl)-4-[3-(triisopropylsiloxy)-3-methyl-1-butynyl]-6-methylindoline (380).**

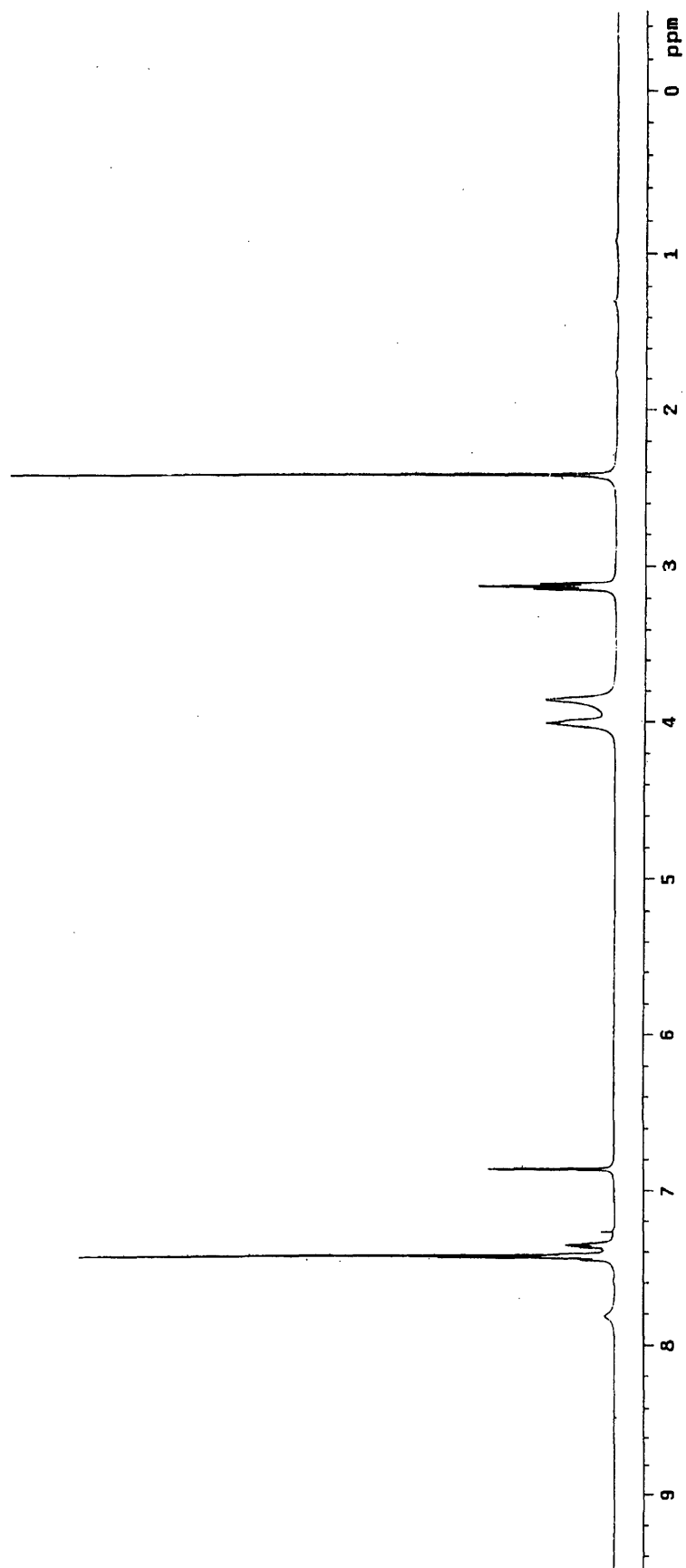
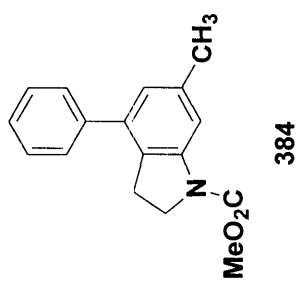
A 25-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with ynamide **356** (0.203 g, 0.472 mmol), BHT (0.104 g, 0.472 mmol), and 9 mL of toluene. The reaction mixture was heated at reflux for 30 h and then allowed to cool to room temperature and concentrated to afford 0.306 g of a pale brown oil. Column chromatography on 35 g of silica gel (elution with toluene) provided 0.170 g (84%) of indoline **380** as a pale yellow oil: IR (neat) 2943, 2865, 2218, 1722, 1589, 1488, and 1446 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.69 (br s, 1H), 6.80 (s, 1H), 4.01 (br s, 2H), 3.82 (s, 3H), 3.09 (t, $J = 8.5$ Hz, 2H), 2.32 (s, 3H), 1.62 (s, 6H), 1.19 (sept, $J = 7.3$ Hz, 3H), and 1.11 (d, $J = 7.3$ Hz, 18H); ^{13}C NMR (125 MHz, CDCl_3) δ 153.7, 142.8, 137.8, 130.7, 126.0, 119.3, 115.6, 98.1, 80.2, 66.7, 52.6, 47.6, 33.6, 27.1, 21.7, 18.5, and 13.1; Anal. Calcd for $\text{C}_{25}\text{H}_{39}\text{NO}_3\text{Si}$: C, 69.88; H, 9.15; N, 3.26. Found: C, 70.04; H, 9.24; N, 3.36.

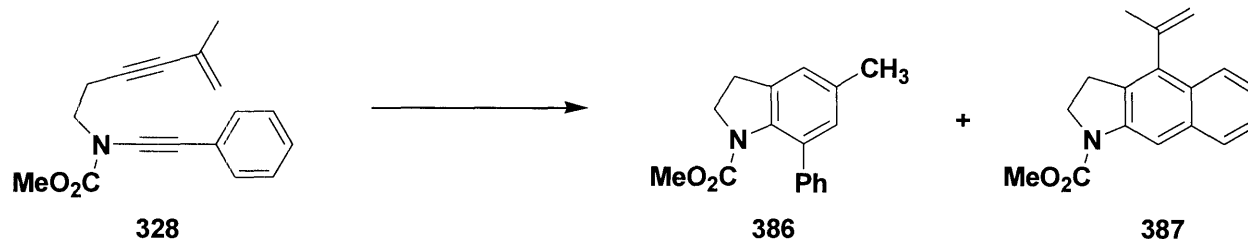




***N*-(Methoxycarbonyl)-6-methyl-4-phenylindoline (**384**).**

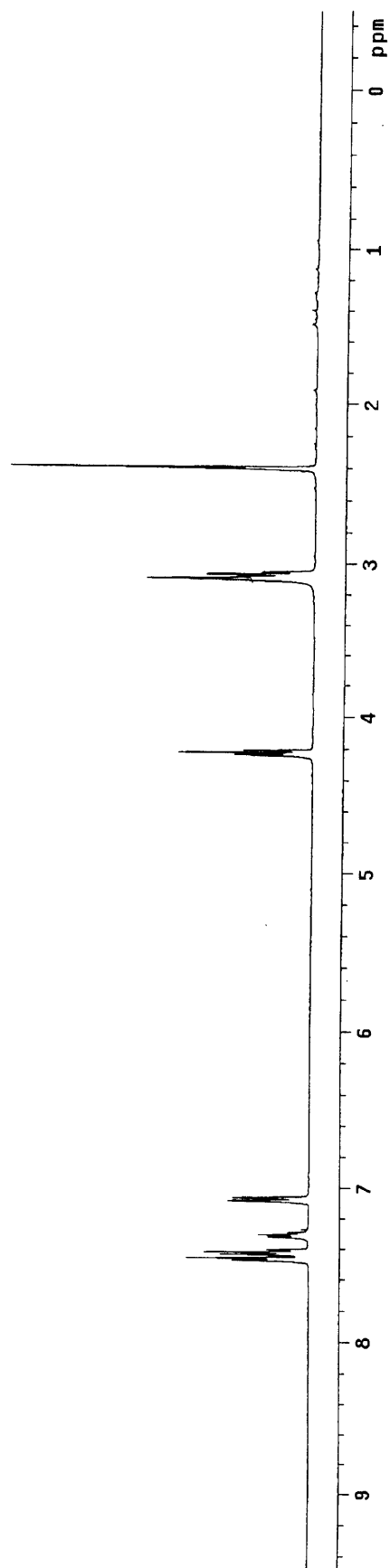
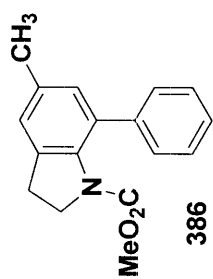
A threaded Pyrex tube (ca. 60 mL capacity) equipped with a rubber septum and argon inlet needle was charged with the enyne **352** (0.152 g, 0.569 mmol), BHT (0.125 g, 0.569 mmol), and 11.4 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles, and the tube was then sealed under argon with a threaded Teflon cap. The reaction mixture was heated in an oil bath at 150 °C for 9 h and then allowed to cool to rt. Concentration afforded 0.261 g of a dark yellow oil. Column chromatography on 80 g (gradient elution with 0–2% EtOAc-hexanes) and then on 40 g of silica gel (elution with 1% EtOAc-hexanes) provided 0.125 g (82%) of indoline **384** as a white solid: mp 86–87 °C; IR (film) 2953, 1717, 1591, 1573, 1446, and 1334 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.82 (br s, 1H), 7.42 (m, 4H), 7.36 (m, 1H), 6.86 (s, 1H), 4.01 (br s, 2H), 3.86 (br s, 3H), 3.12 (t, *J* = 8.5 Hz, 2H), and 2.42 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 153.7, 143.2, 140.6, 138.3, 138.1, 128.5, 128.3, 127.2, 125.8, 124.1, 114.6, 52.6, 48.0, 27.2, and 21.8; HRMS-ESI *m/z*: [M+H]⁺ calcd for C₁₇H₁₇NO₂, 268.1332; found, 268.1330.

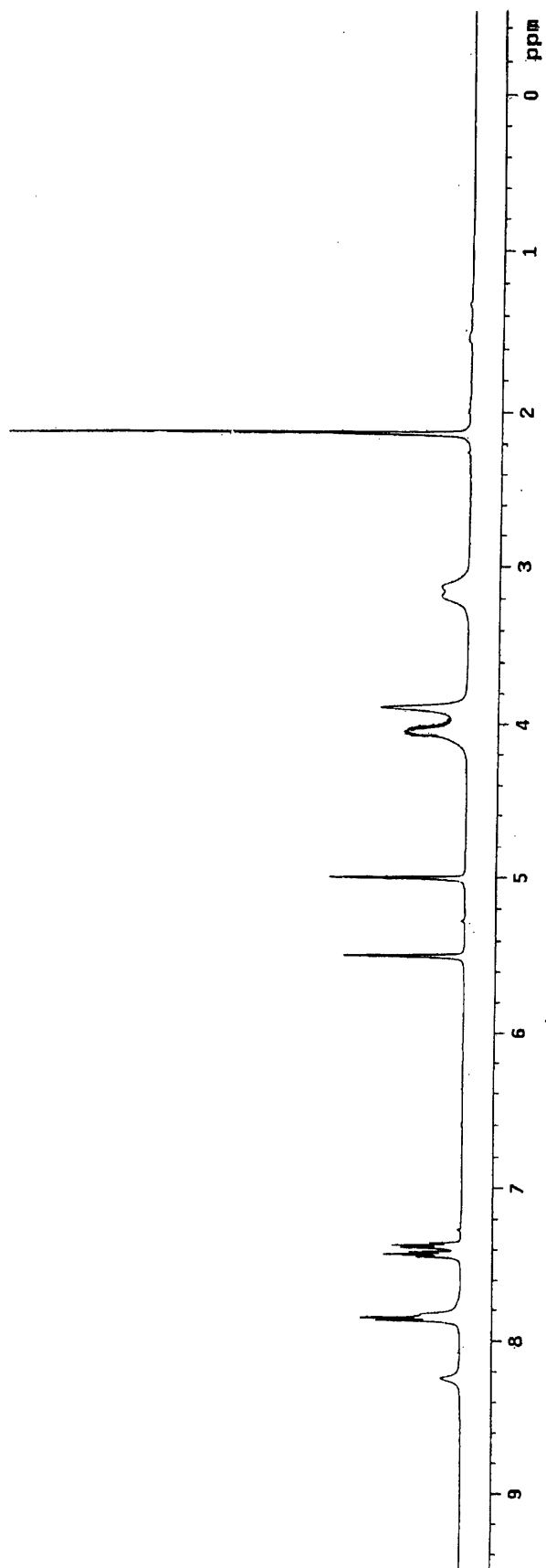
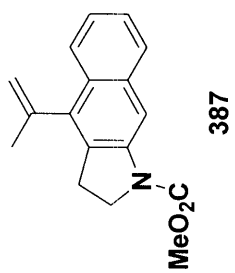


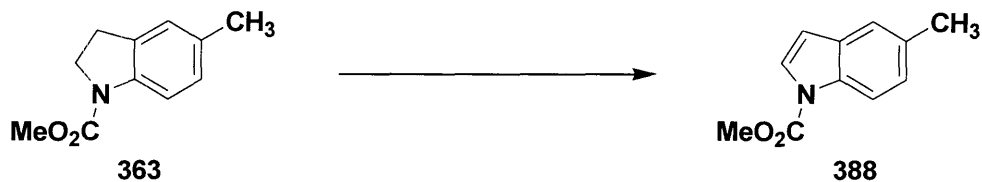


***N*-(Methoxycarbonyl)-5-methyl-7-phenylindoline (386) and *N*-(Methoxycarbonyl)-4-isopropenylbenzo[*f*]indoline (387).**

A threaded Pyrex tube (ca. 60 mL capacity) equipped with a rubber septum and argon inlet needle was charged with the ynamide **328** (0.307 g, 1.15 mmol), BHT (0.256 g, 1.16 mmol), and 23 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles, and the tube was then sealed under argon with a threaded Teflon cap. The reaction mixture was heated in an oil bath at 150 °C for 9 h and then allowed to cool to rt. Concentration afforded 0.789 g of a yellow oil. Column chromatography on 40 g of silica gel (gradient elution with 0–10% EtOAc-hexanes) provided 0.091 g (30%) of indoline **386** as a white solid and 0.183 g (59%) of benzoindoline **387** as a white solid. For **386**: mp 93–94 °C; IR (CDCl₃) 2954, 2920, 1685, 1603, 1444, 1411, 1368, 1342, 1251, 1198, 1123, 1016, and 903 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.41–7.48 (m, 4H) 7.31 (m, 1H), 7.06–7.09 (m, 2H), 4.22 (t, *J* = 7.7 Hz, 2H), 3.10 (s, 3H), 3.07 (t, *J* = 7.7 Hz, 2H), and 2.39 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 154.4, 141.8, 137.3, 135.2, 134.6, 131.1, 129.8, 128.5, 126.9, 126.6, 124.5, 52.0, 50.5, 29.4, and 21.1; GC-MS *m/z*: 267 (M⁺); Anal. Calcd for C₁₇H₁₇NO₂: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.21; H, 6.57; N, 5.18. For **387**: mp 126–128 °C; IR (film) 3073, 2966, 1717, 1621, 1606, 1462, 1373, 1359, 1329, 1197, 1138, 1047, 875, and 751 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.25 (br s, 1H), 7.83–7.87 (m, 2H), 7.43 (app dd, *J* = 7.0, 7.8 Hz, 1H), 7.38 (app dd, *J* = 7.0, 7.8 Hz, 1H), 5.50 (s, 1H), 5.00 (s, 1H), 4.05 (br s, 2H), 3.89 (br s, 3H), 3.13 and 3.19 (rotamers, br s, 2H), and 2.13 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 153.7, 142.6, 140.3, 137.6, 134.3, 128.6, 128.1, 128.1, 125.6, 124.9, 124.2, 116.4, 109.7, 52.6, 47.5, 26.4, and 23.7; GC-MS *m/z*: 267 (M⁺); Anal. Calcd for C₁₇H₁₇NO₂: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.29; H, 6.24; N, 5.25.

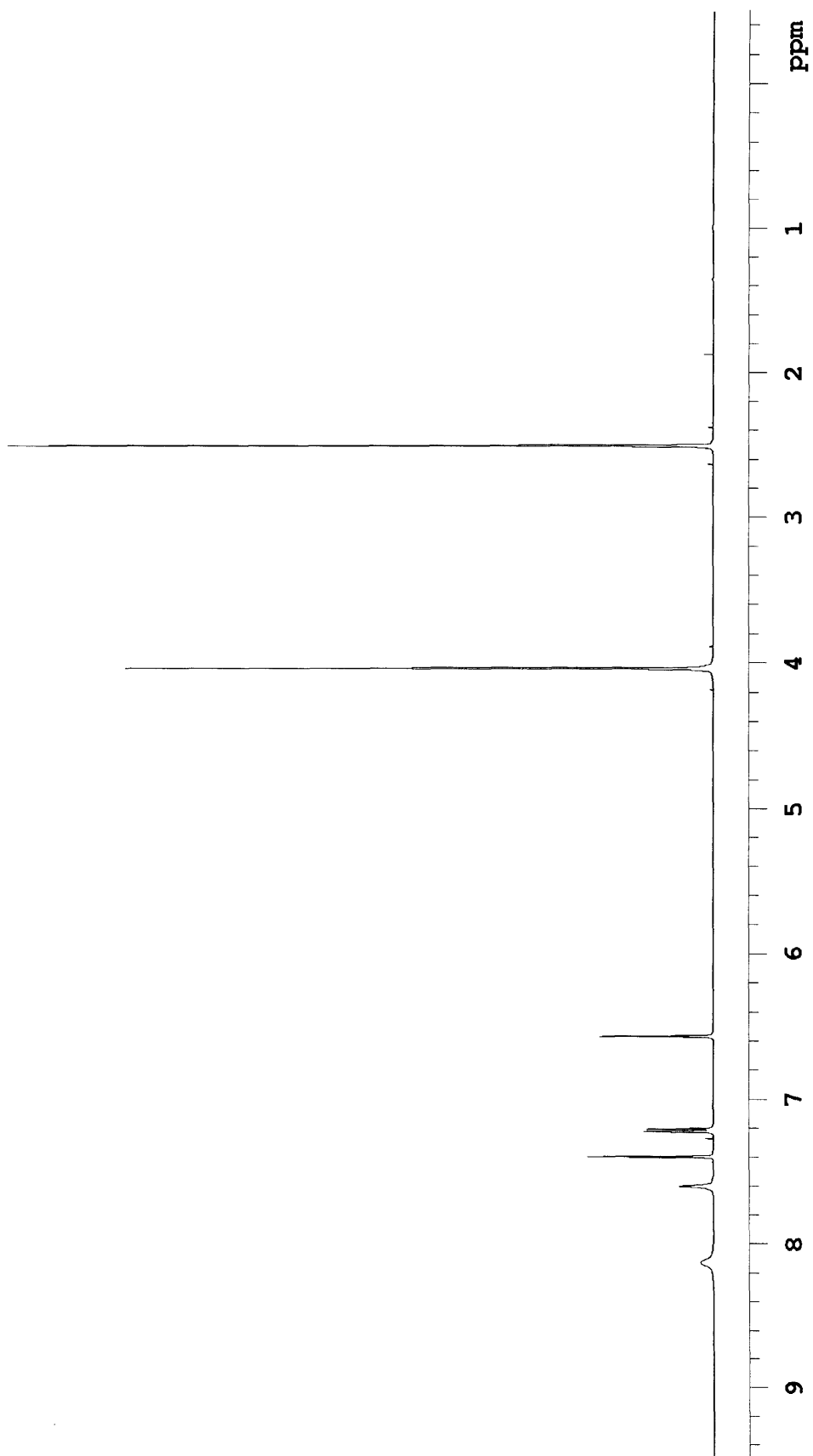
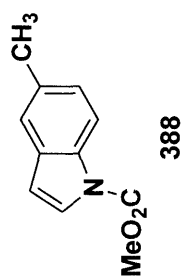


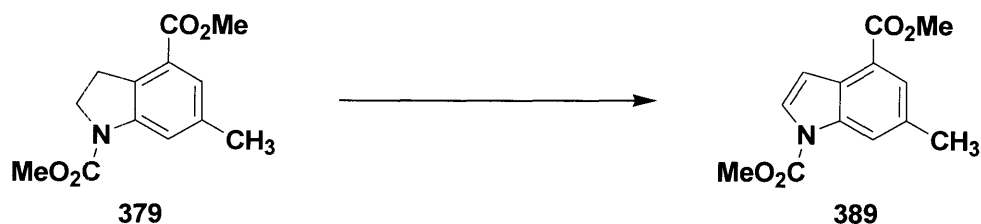




***N*-(Methoxycarbonyl)-5-methylindole (388).**

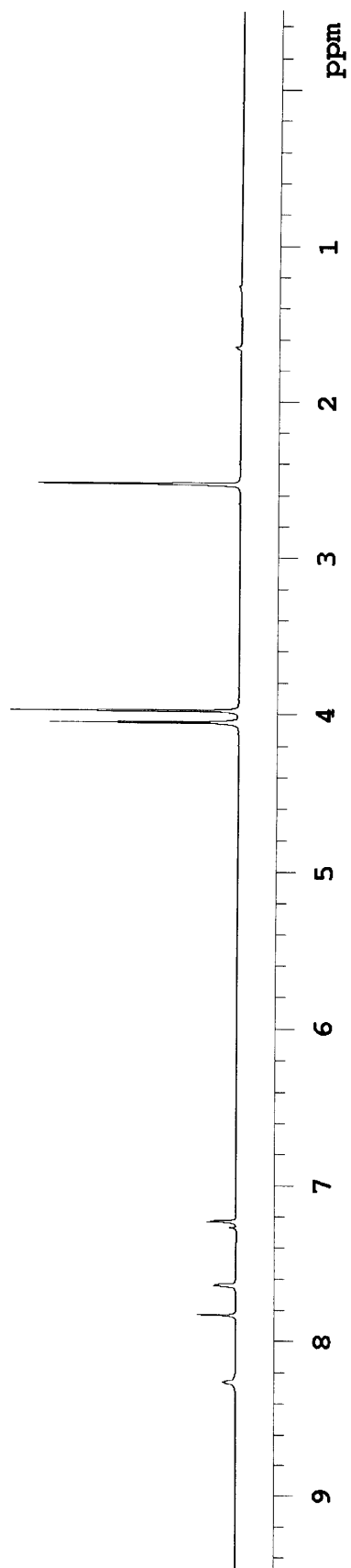
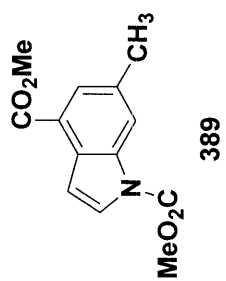
A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with indoline **363** (0.215 g, 1.12 mmol) and 3.7 mL of benzene. *o*-Chloranil (0.553 g, 2.25 mmol) was added in one portion and the resulting dark purple suspension was stirred at rt for 48 h. The reaction mixture was then filtered through a column of alumina (5 x 1.5 cm) with the aid of 500 mL of 10% EtOAc-hexanes. Concentration of the filtrate afforded 0.215 g of a dark red oil. Column chromatography on 100 g of silica gel (elution with 3% EtOAc-hexanes) provided 0.180 g (85%) of indole **388** as a very pale red solid: mp 54–55 °C; IR (CH₂Cl₂) 3149, 2918, 1737, 1613, 1586, 1535, 1462, and 1450 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.13 (br s, 1H), 7.60 (br s, 1H), 7.40 (s, 1H), 7.21 (app dd, *J* = 1.2, 8.5 Hz, 1H), 6.57 (d, *J* = 3.7 Hz, 1H), 4.04 (s, 3H), and 2.51 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 151.5, 133.4, 132.5, 130.7, 125.9, 125.5, 121.0, 114.7, 107.9, 53.7, and 21.3; Anal. Calcd for C₁₁H₁₁NO₂: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.98; H, 5.62; N, 7.36.

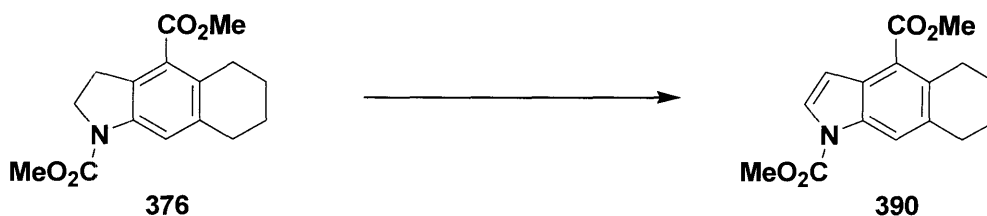




***N*-(Methoxycarbonyl)-4-methoxycarbonyl-6-methylindole (389).**

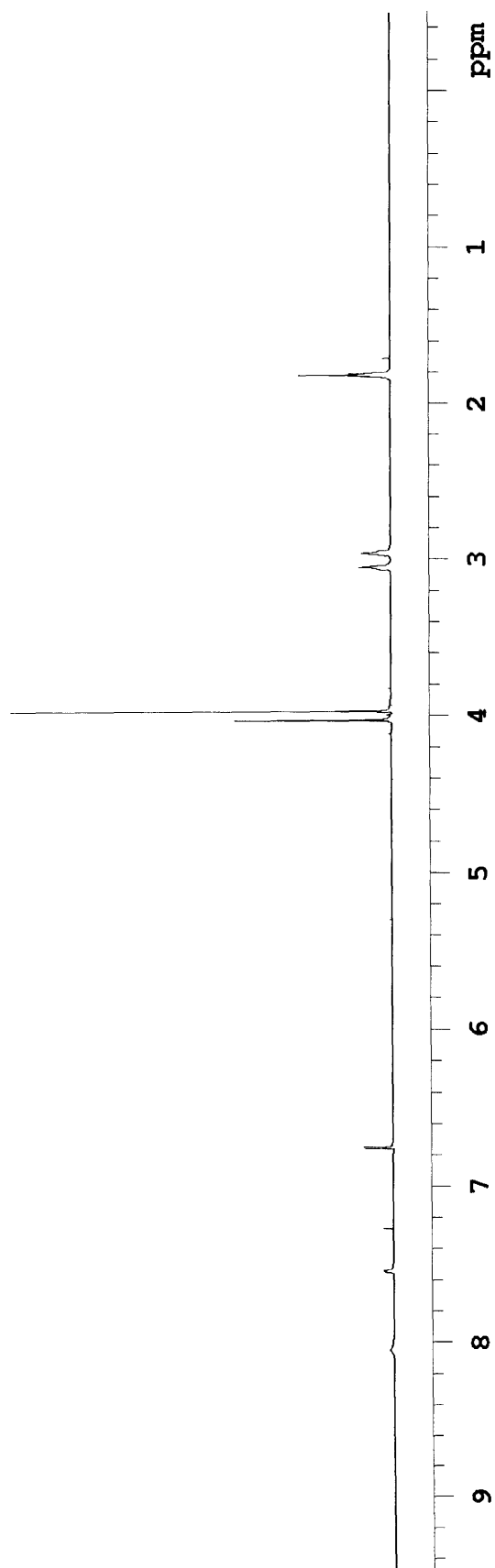
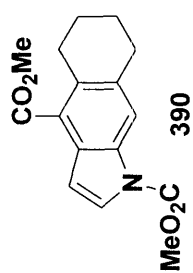
A threaded Pyrex tube (ca. 20 mL capacity) equipped with a rubber septum and argon inlet needle was charged with indoline **379** (0.029 g, 0.12 mmol) and 0.8 mL of benzene. *o*-Chloranil (0.057 g, 0.23 mmol) was added in one portion and the resulting dark purple suspension was stirred at rt for 160 h. The reaction mixture was then filtered through a column of silica gel (9 x 1.5 cm) with the aid of 300 mL of 10% EtOAc-hexanes. Concentration of the filtrate afforded 0.047 g of an orange-red solid. Column chromatography on 40 g of silica gel (elution with 5% EtOAc-hexanes) provided 0.022 g (77%) of indole **389** as a white solid: mp 81–82 °C; IR (film) 3136, 2957, 1742, 1714, 1612, 1582, 1528, and 1443 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.27 (br s, 1H), 7.83 (dd, *J* = 0.6, 1.5 Hz, 1H), 7.64 (d, *J* = 3.7 Hz, 1H), 7.23 (dd, *J* = 0.6, 3.7 Hz, 1H), 4.05 (s, 3H), 3.98 (s, 3H), and 2.53 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 167.6, 151.5, 136.5, 134.3, 128.4, 127.2, 126.8, 121.8, 120.1, 108.8, 54.1, 52.1, and 21.9; HRMS-ESI *m/z*: [M+Na]⁺ calcd for C₁₃H₁₃NO₄, 270.0737; found, 270.0733.





***N*-(Methoxycarbonyl)-4-methoxycarbonyl-5,6,7,8-tetrahydrobenzo[*f*]indole (390).**

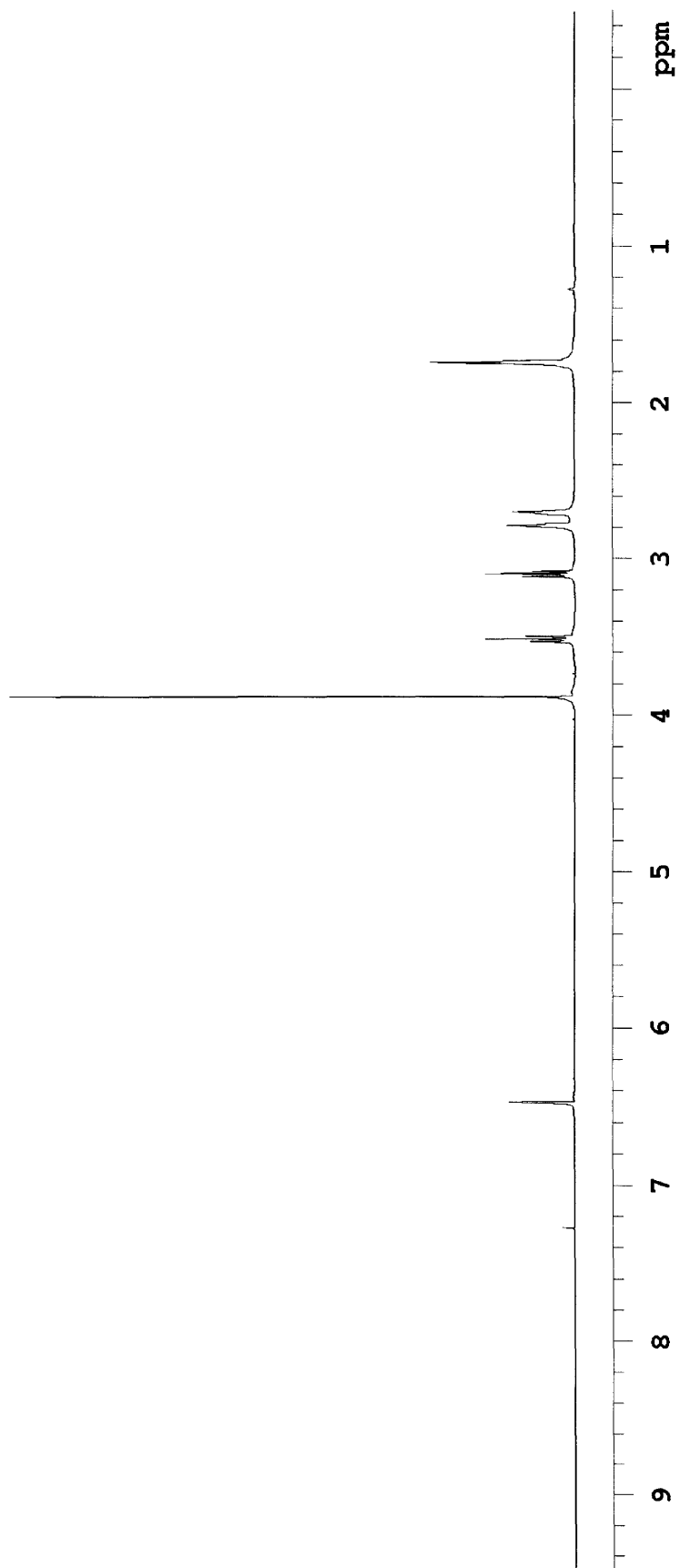
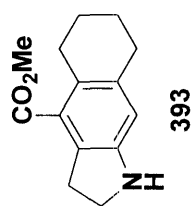
A threaded Pyrex tube (ca. 20 mL capacity) equipped with a rubber septum and argon inlet needle was charged with indoline **376** (0.172 g, 0.594 mmol) and 2.2 mL of benzene. *o*-Chloranil (0.292 g, 1.19 mmol) was added in one portion and the resulting dark purple suspension was stirred at rt for 120 h. The reaction mixture was then filtered through a column of silica gel (5 x 3 cm) with the aid of 750 mL of 10% EtOAc-hexanes. Concentration of the filtrate afforded 0.373 g of a dark red solid. Column chromatography on 40 g of silica gel (gradient elution with 5–10% EtOAc-hexanes) provided 0.070 g (41%) of indole **390** as a white solid: mp 104–106 °C; IR (film) 3136, 2935, 2858, 1742, 1721, 1611, 1573, 1531, and 1444 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.05 (br s, 1H), 7.54 (app d, *J* = 3.8 Hz, 1H), 6.75 (dd, *J* = 0.8, 3.8 Hz, 1H), 4.03 (s, 3H), 3.97 (s, 3H), 3.05 (m, 2H), 2.96 (m, 2H), and 1.82 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 168.8, 151.5, 135.2, 133.9, 133.2, 128.3, 126.0, 123.0, 118.3, 108.2, 54.0, 51.9, 31.1, 27.9, 23.4, and 22.9; HRMS-ESI *m/z*: [M+Na]⁺ calcd for C₁₆H₁₇NO₄, 310.1050; found, 310.1045.





4-Methoxycarbonyl-5,6,7,8-tetrahydrobenzo[f]indoline (**393**).

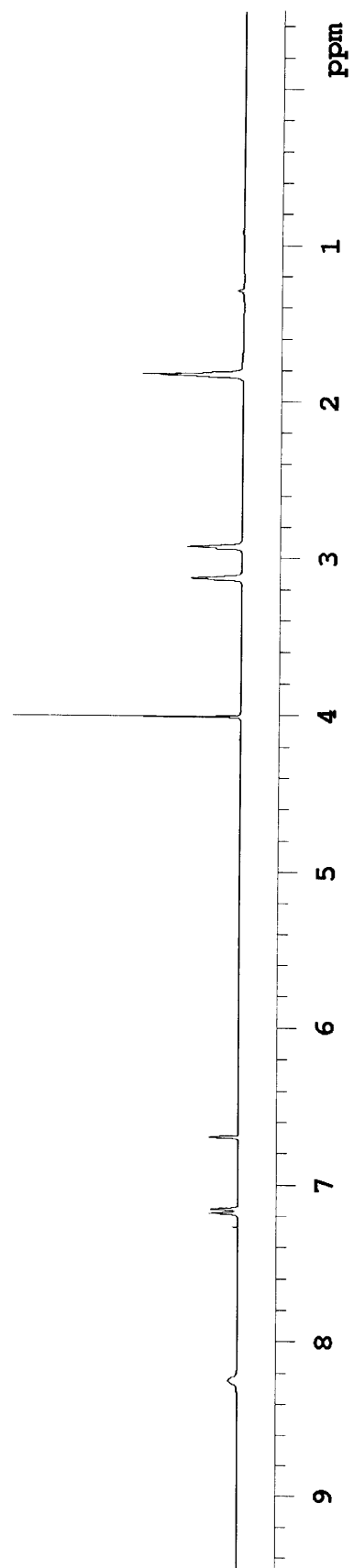
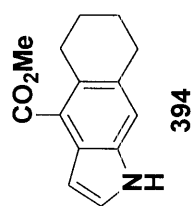
A threaded Pyrex tube (ca. 20 mL capacity) equipped with a rubber septum and argon inlet needle was charged with indoline **377** (0.080 g, 0.24 mmol) and 1.8 mL of CH₂Cl₂. Trifluoroacetic acid (0.55 mL, 0.81 g, 7.1 mmol) was added via syringe in one portion, and the resulting light brown solution was stirred at rt for 2 h. The reaction mixture was then diluted with 25 mL of Et₂O and extracted with 25 mL of satd NaHCO₃ solution. The aqueous layer was extracted with two 15-mL portions of Et₂O, and the combined organic layers were washed with 20 mL of satd NaCl solution, dried over MgSO₄, filtered, and concentrated to provide 0.059 g of a pale orange oil. Column chromatography on 40 g of silica gel (gradient elution with 10–20% EtOAc-hexanes) provided 0.054 g (97%) of indoline **393** as a beige solid: mp 48–50 °C; IR (film) 3377, 2929, 2855, 1720, 1611, and 1437 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.47 (s, 1H), 3.88 (s, 3H), 3.51 (t, *J* = 8.3 Hz, 2H), 3.09 (t, *J* = 8.3 Hz, 2H), 2.78 (m, 2H), 2.70 (m, 2H), and 1.74 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 169.5, 149.6, 137.1, 128.7, 127.7, 126.0, 112.4, 51.7, 47.4, 30.5, 30.3, 27.2, 23.6, and 23.0; HRMS-ESI *m/z*: [M+H]⁺ calcd for C₁₄H₁₇NO₂, 232.1332; found, 232.1340.





4-Methoxycarbonyl-5,6,7,8-tetrahydrobenzo[f]indole (**394**).

A threaded Pyrex tube (ca. 20 mL capacity) equipped with a rubber septum and argon inlet needle was charged with indoline **393** (0.053 g, 0.23 mmol) and 3.2 mL of benzene. *o*-Chloranil (0.057 g, 0.23 mmol) was added in one portion and the resulting dark purple solution was stirred at rt for 15 min. The reaction mixture was then diluted with 25 mL of Et₂O and washed with two 20-mL portions of half-satd Na₂CO₃ solution. The combined aqueous layers were extracted with two 20-mL portions of Et₂O, and the combined organic layers were washed with 25 mL of satd NaCl solution, dried over MgSO₄, filtered, and concentrated to provide 0.067 g of a dark green solid. Column chromatography on 40 g of silica gel (gradient elution with 10–30% EtOAc-hexanes) provided 0.046 g (88%) of indole **394** as a white solid: mp 90–92 °C; IR (film) 3409, 2930, 2856, 1696, 1620, and 1434 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.25 (br s, 1H), 7.18 (s, 1H), 7.15 (app s, 1H), 6.70 (app s, 1H), 4.01 (s, 3H), 3.12 (m, 2H), 2.93 (m, 2H), and 1.83 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 169.9, 134.9, 132.3, 130.7, 125.9, 125.3, 121.9, 114.5, 102.7, 51.8, 30.9, 27.9, 23.7, and 23.1; HRMS-ESI *m/z*: [M+Na]⁺ calcd for C₁₄H₁₅NO₂, 252.0995; found, 252.0992.



Experimental Section for Part II

General Procedures. All reactions were performed in the 25-mL Thar stainless steel view cell reactor (model 05422-2) shown in Figure 1. A schematic flow diagram of the experimental apparatus is in Figure 2. This reactor allows visual inspection via two 1-inch coaxial sapphire windows. Cell pressures and temperatures were monitored with a Swagelok industrial pressure gauge (0–350 bar range, accuracy of ± 5 bar) and Omega K-type low-noise thermocouple probe (accuracy of ± 1 °C). Temperature set-points were attained using an Omega miniature autotune temperature controller in PID mode (series CN9000A) in conjunction with a Powerstat variable autotransformer (type 3PN116B) and Omega insulated heating tape (model #STH051-060) wrapped tightly about the exterior cell wall. The reactor was purged with argon before pressurizing with CO₂ and the reactor contents were mixed using a magnetic stir bar. Reaction product solutions and chromatography fractions were concentrated by rotary evaporation at ca. 20 mmHg and then at ca. 0.1 mmHg (vacuum pump) unless otherwise indicated. Thin layer chromatography was performed on Merck precoated glass-backed silica gel 60 F-254 0.25 mm plates. Column chromatography was performed on EM Science silica gel 60 or Silicycle silica gel 60 (230–400 mesh).

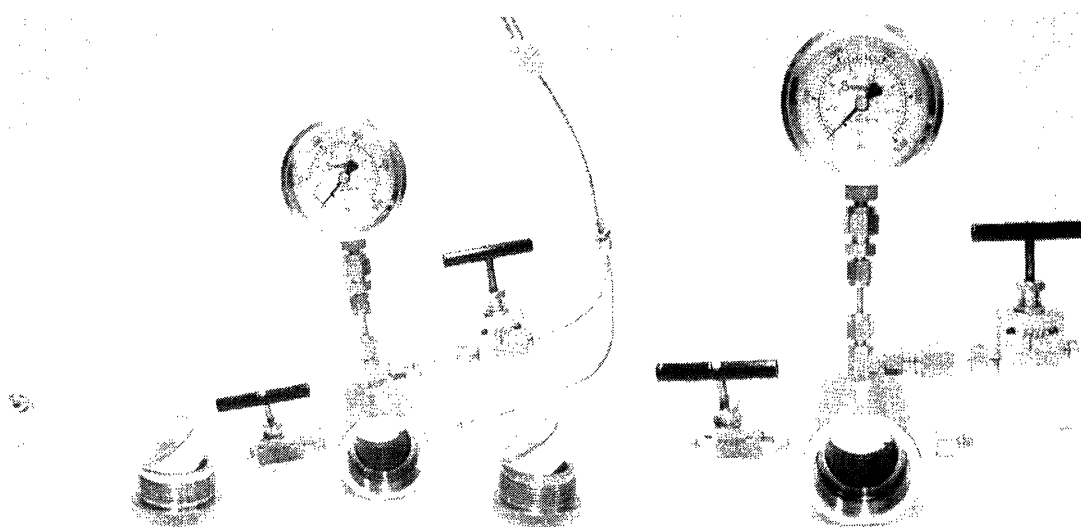


Figure 1. Thar stainless steel view cell reactor (model 05422-2).

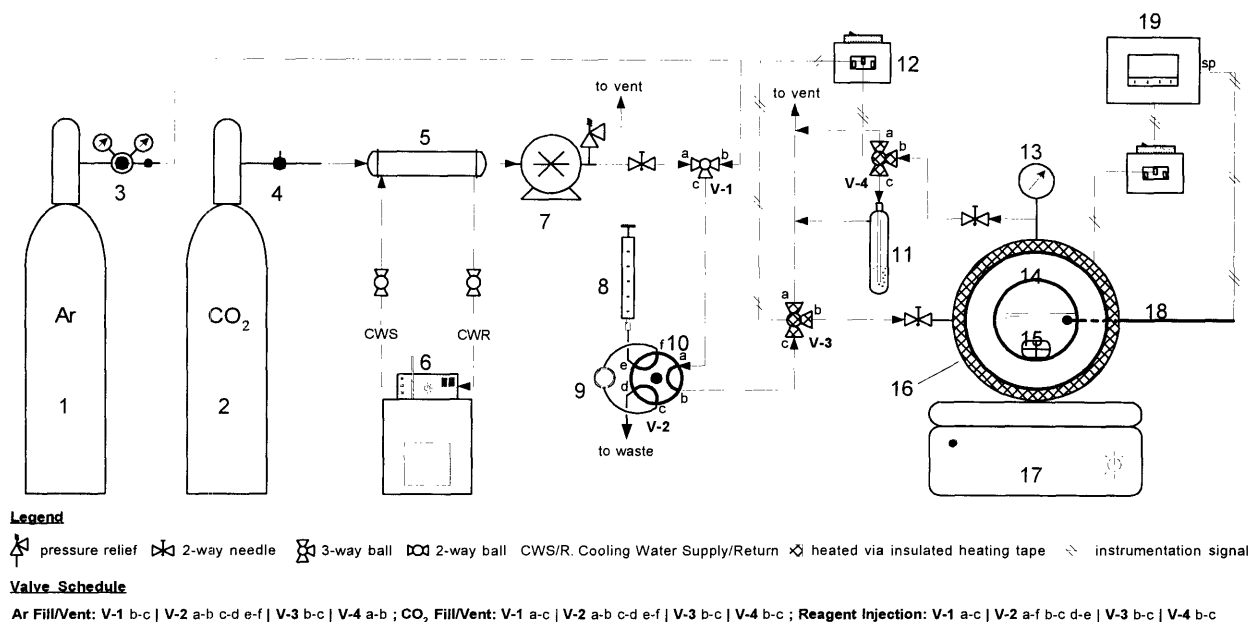


Figure 2. Schematic flow diagram of the experimental apparatus. (1) argon gas cylinder; (2) carbon dioxide liquid cylinder; (3) gas regulator; (4) SFC/SFE transfer kit; (5) shell-and-tube heat exchanger; (6) cooled circulating bath; (7) metering pump; (8) syringe; (9) sample loop; (10) 6-way valve; (11) sparge chamber; (12) variable autotransformer; (13) pressure gauge; (14) view cell; (15) stir bar; (16) insulated heating tape; (17) stir plate; (18) thermocouple; (19) temperature controller.

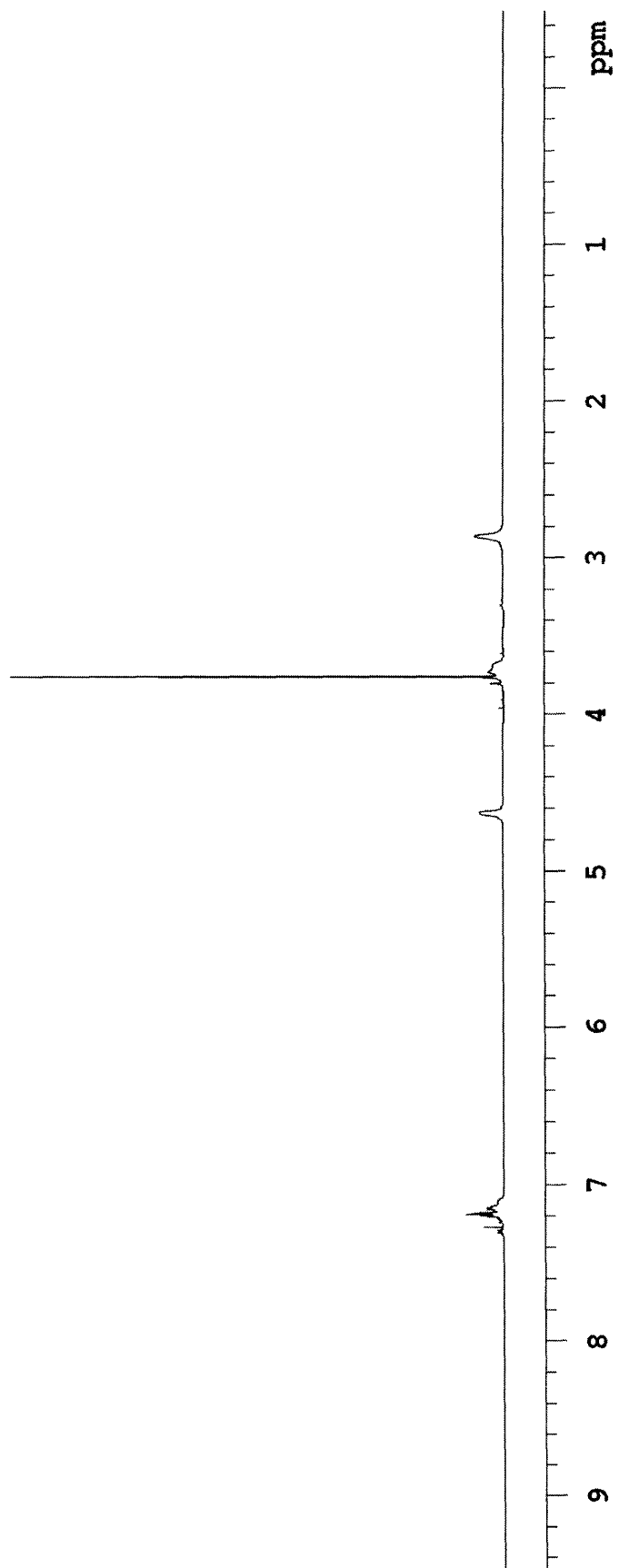
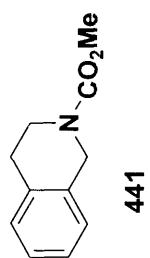
Materials. Commercial grade reagents were used without further purification except as indicated below. Isobutyraldehyde and propionaldehyde were distilled under argon. Carbon dioxide (99.9995%) was purchased from Airgas. Aqueous solutions of H₂SO₄ and TFA were prepared by adding the acid to deionized water.

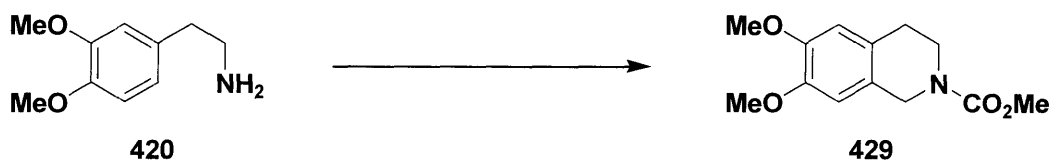
Instrumentation. The melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained using a Perkin Elmer 2000 FT-IR spectrophotometer. ¹H NMR and ¹³C NMR spectra were measured with an Inova 500 spectrometer. ¹H NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the CHCl₃ peak at 7.27 ppm used as a standard). ¹³C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the central peak of CHCl₃ at 77.23 ppm used as a standard). Low resolution mass spectra (GC-MS) were measured on a Agilent 6890N series gas chromatograph with Agilent 5973 series mass selective detection. High resolution mass spectra (HRMS) were measured on a Bruker Daltonics APEXII 3 Tesla Fourier transform mass spectrometer.



General Procedure A for the Two-Stage Reaction Using Sulfuric Acid to Promote Pictet-Spengler Cyclization. *N*-(Methoxycarbonyl)-1,2,3,4-Tetrahydroisoquinoline (441).

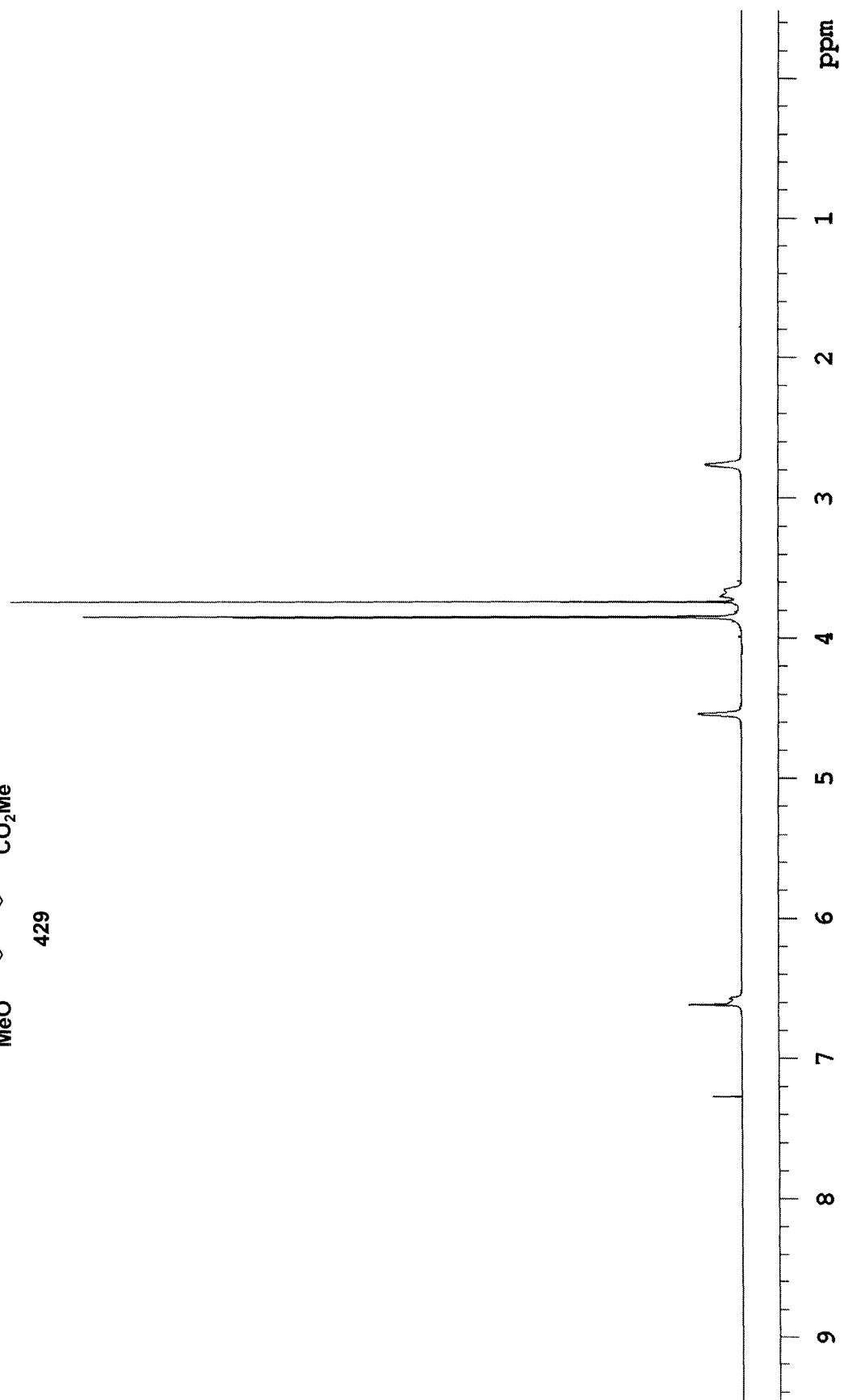
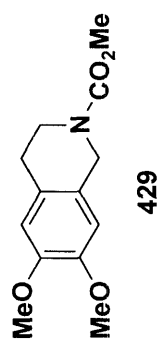
A 25-mL, stainless steel Thar view cell reactor was charged with phenethylamine (**439**) (1.6 mL, 1.5 g, 13 mmol) and dimethyl carbonate (2.2 mL, 2.4 g, 26 mmol), pressurized to 50 bar with CO₂, heated to 130 °C, and then pressurized with additional CO₂ to 120 bar. The biphasic reaction mixture was stirred at 130 °C (120–130 bar) for 24 h. The reactor was allowed to cool to 80 °C and formaldehyde (1.5 mL, 13 M in H₂O, 20 mmol) and H₂SO₄ (2.0 mL, 9.0 M in H₂O, 18 mmol) were added sequentially via the 2-mL sample loop (depicted in Figure 2 as #9). The resulting triphasic reaction mixture was stirred at 80 °C (140–160 bar) for 24 h. The reactor was cooled to rt, the CO₂-phase was sparged into a biphasic mixture containing 15 mL of CH₂Cl₂ and 15 mL of water, and the remaining reactor contents were dissolved in 100 mL of CH₂Cl₂ and 100 mL of water. The aqueous layer was separated from the combined organic layers and extracted with three 75-mL portions of CH₂Cl₂. The combined organic layers were washed with 150 mL of satd NaCl solution, dried over MgSO₄, filtered, and concentrated to afford 1.925 g of a dark yellow oil. Column chromatography on 90 g of silica gel (gradient elution with 10–15% EtOAc-hexanes) provided 1.271 g (52%) of tetrahydroisoquinoline **441** as a colorless oil: IR (neat) 2953, 1709, 1605, and 1449 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.10–7.32 (m, 4H), 4.63 (br s, 2H), 3.76 (s, 3H), 3.70 (m, 2H), and 2.86 (br s, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 156.2, 134.6 (and rotamer 134.8), 133.3 (and rotamer 133.6), 128.8 (and rotamer 129.0), 128.7, 126.5, 126.4 (and rotamer 126.7), 52.9, 45.9, 41.5 (and rotamer 41.7), and 28.9 (and rotamer 29.2); GC-MS *m/z*: 191 (M⁺).

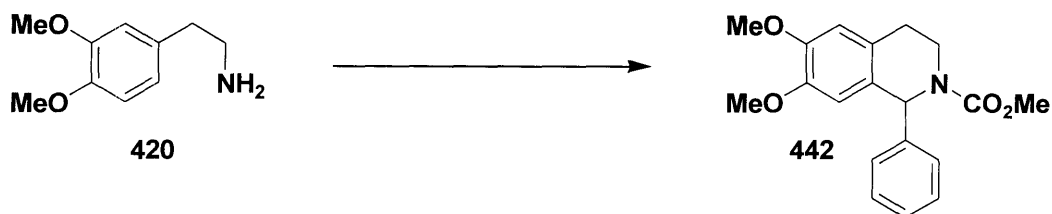




***N*-(Methoxycarbonyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (429).**

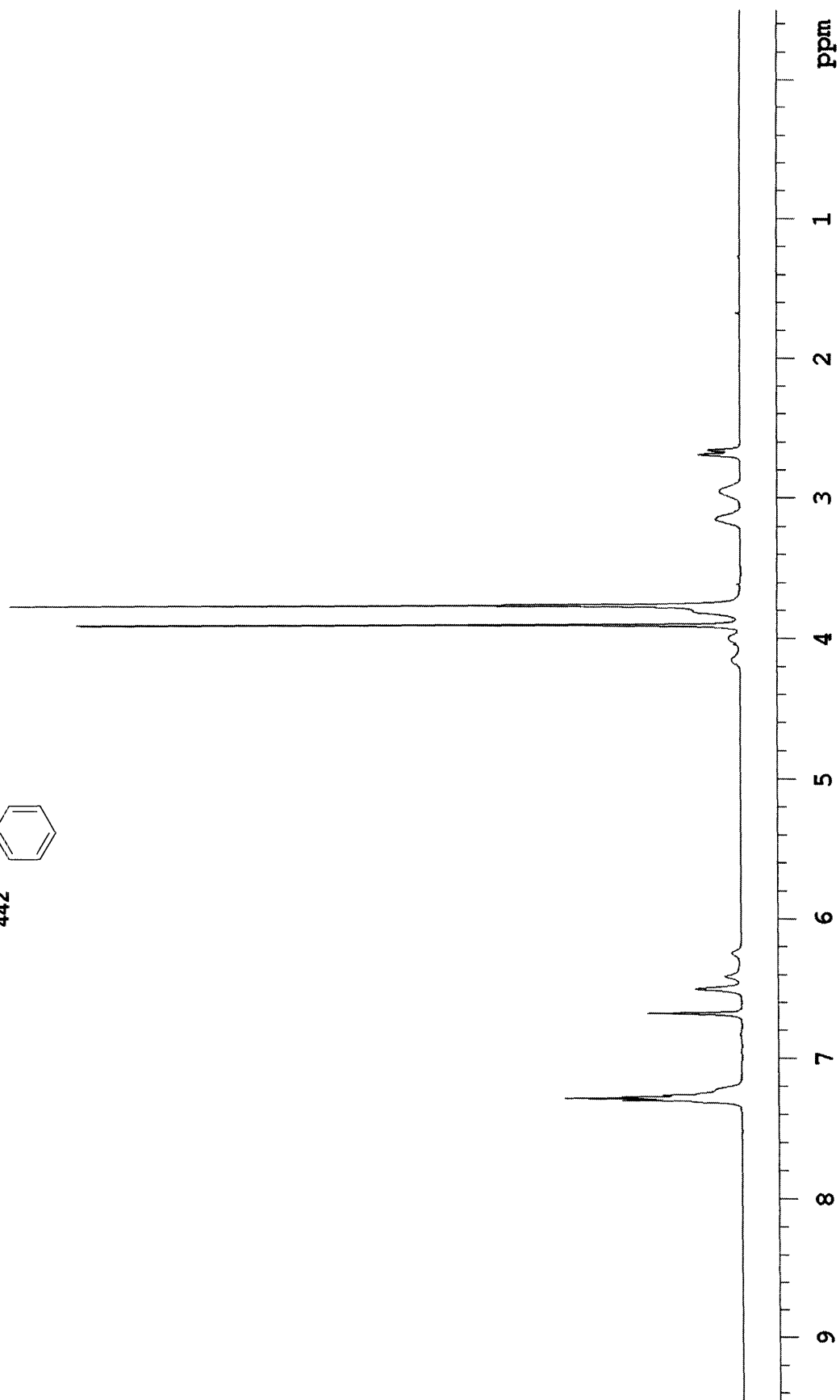
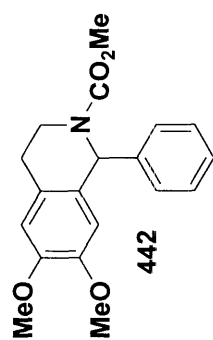
Reaction of amine **420** (2.1 mL, 2.3 g, 13 mmol), DMC (2.1 mL, 2.2 g, 25 mmol), formaldehyde (1.5 mL, 13 M in H₂O, 20 mmol) and H₂SO₄ (2.0 mL, 9.0 M in H₂O, 18 mmol) according to General Procedure A afforded 3.291 g of a dark brown oil. Column chromatography on 120 g of silica gel (gradient elution with 5–50% EtOAc-hexanes) provided 1.710 g (54%) of tetrahydroisoquinoline **429** as a colorless oil: IR (neat) 2953, 1710, 1691, 1612, and 1513 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.61 (s, 1H), 6.58 (m, 1H), 4.54 (br s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.74 (s, 3H), 3.65–3.70 (m, 2H), and 2.76 (br s, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 155.9, 147.53, 147.49, 126.0 (and rotamer 126.3), 124.7 (and rotamer 125.1), 111.3 (and rotamer 111.4), 108.8 (and rotamer 109.0), 55.82, 55.79, 52.5, 45.3, 41.3 (and rotamer 41.5), and 28.1 (and rotamer 28.3); GC-MS *m/z*: 251 (M⁺).

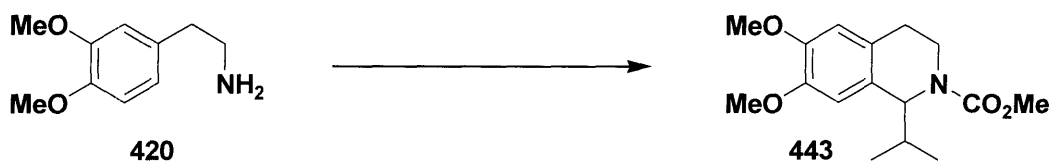




***N*-(Methoxycarbonyl)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (442).**

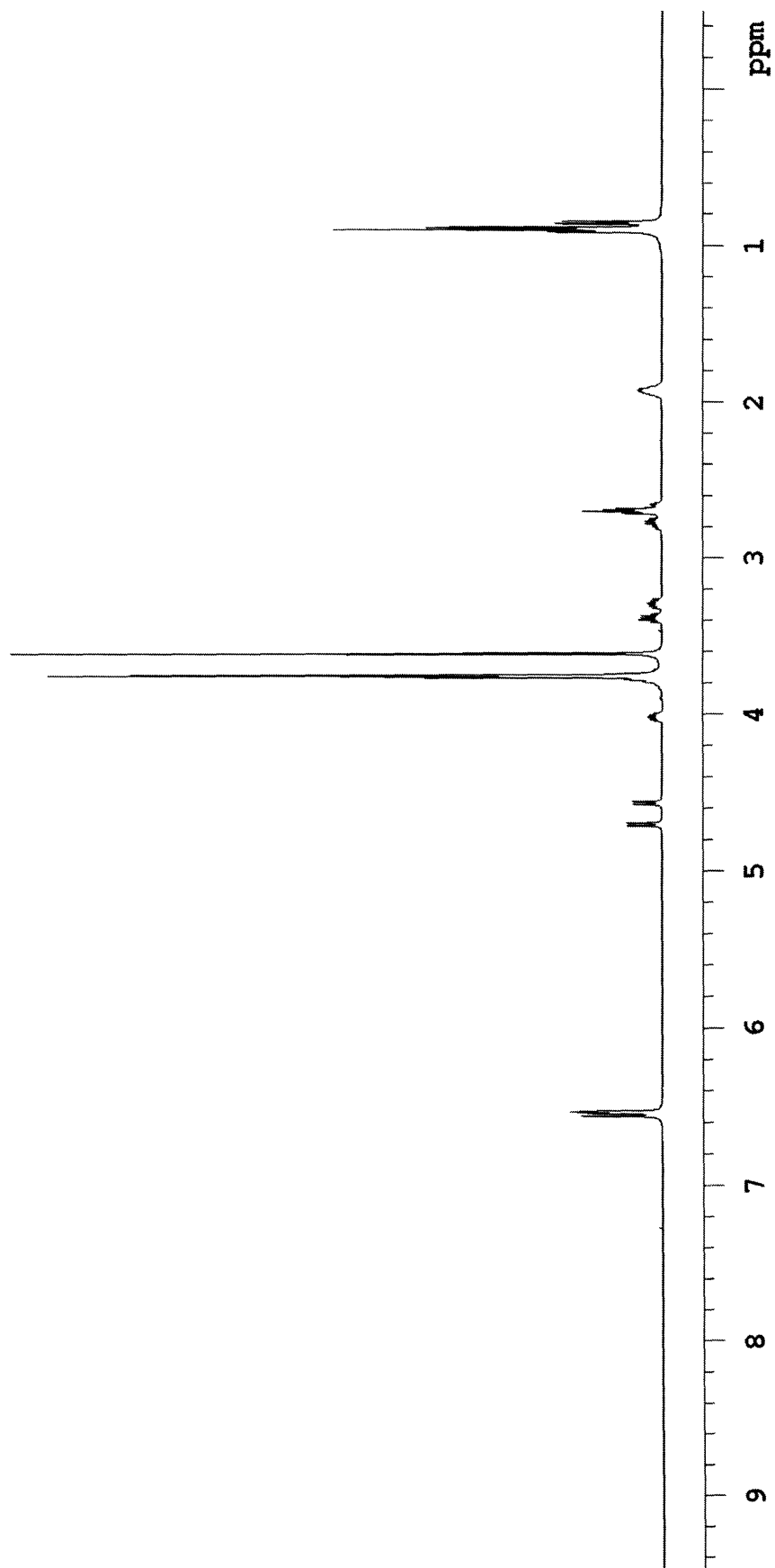
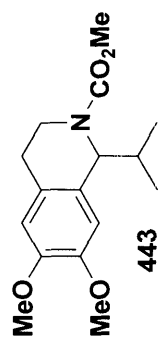
Reaction of amine **420** (2.1 mL, 2.3 g, 13 mmol), DMC (2.1 mL, 2.2 g, 25 mmol), benzaldehyde (2.0 mL, 2.1 g, 20 mmol) and H₂SO₄ (2.0 mL, 9.0 M in H₂O, 18 mmol) according to General Procedure A afforded 4.150 g of a brown oil. Column chromatography on 140 g of silica gel (elution with 30% EtOAc-hexanes) provided 2.300 g (56%) of tetrahydroisoquinoline **442** as a white solid: mp 98–100 °C; IR (film) 2952, 1703, 1692, 1611, 1515, and 1444 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.24–7.31 (m, 5H), 6.67 (s, 1H), 6.50 (s, 1H), 6.41 (rotamer, br s, 0.5H), 6.24 (rotamer, br s, 0.5H), 4.15 (rotamer, br s, 0.5H), 4.00 (rotamer, br s, 0.5H), 3.89 (s, 3H), 3.76 (s, 6H), 3.15 (br s, 1H), 2.94 (br s, 1H), 2.69 (rotamer, br s, 0.5H), and 2.66 (rotamer, br s, 0.5H); ¹³C NMR (125 MHz, CDCl₃) δ 156.0, 148.2, 147.6, 142.7, 128.8, 128.7, 128.4, 127.6, 127.1, 111.3, 111.2, 57.3 (and rotamer 57.4), 56.12, 56.06, 52.9, 37.7 (and rotamer 37.9), and 28.0 (and rotamer 28.2); GC-MS *m/z*: 327 (M⁺).

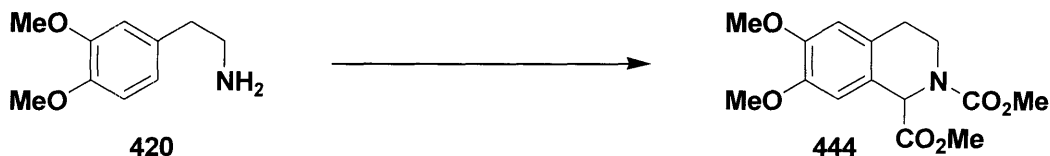




***N*-(Methoxycarbonyl)-1-isopropyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**443**).**

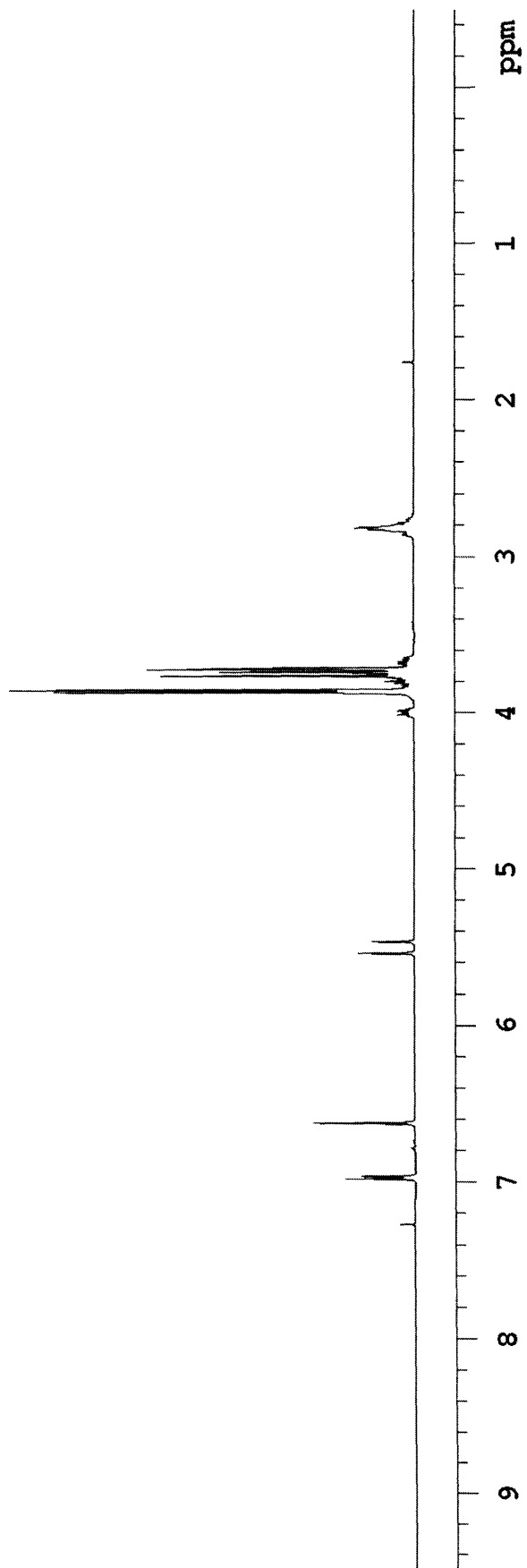
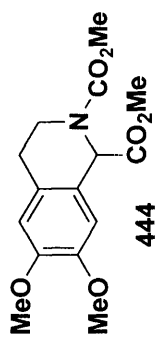
Reaction of amine **420** (2.1 mL, 2.3 g, 13 mmol), DMC (2.1 mL, 2.2 g, 25 mmol), isobutyraldehyde (1.7 mL, 1.3 g, 19 mmol) and H₂SO₄ (2.0 mL, 9.0 M in H₂O, 18 mmol) according to General Procedure A afforded 2.882 g of a dark orange oil. Column chromatography on 160 g of silica gel (gradient elution with 20–30% EtOAc-hexanes) provided 1.975 g (53%) of tetrahydroisoquinoline **443** as a colorless oil: IR (neat) 2958, 1698, 1611, 1518, and 1446 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.52–6.56 (m, 2H), 4.70 (rotamer, d, *J* = 8.5 Hz, 0.5H), 4.57 (rotamer, d, *J* = 8.5 Hz, 0.5H), 4.02 (rotamer, app quint, *J* = 6.1 Hz, 0.5H), 3.76 (s, 6H), 3.61 (s, 3H), 3.38 (rotamer, dt, *J* = 13.0, 6.9 Hz, 0.5H), 3.29 (rotamer, ddd, *J* = 5.8, 8.9, 13.1 Hz, 0.5H), 2.78 (m, 0.5H), 2.66–2.71 (m, 2H), 1.92 (m, 1H), and 0.84–0.91 (m, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 156.3 (and rotamer 156.6), 147.5 (and rotamer 147.6), 146.49 (and rotamer 146.53), 128.5 (and rotamer 129.0), 126.1 (and rotamer 126.3), 111.3 (and rotamer 111.4), 111.0 (and rotamer 111.1), 60.1 (and rotamer 60.2), 55.79 (and rotamer 55.83), 55.7, 52.3 (and rotamer 52.4), 39.0 (and rotamer 39.5), 33.77 (and rotamer 33.81), 27.1 (and rotamer 27.4), 20.1 (and rotamer 20.2), and 19.5 (and rotamer 19.6); GC-MS *m/z*: 293 (M⁺).

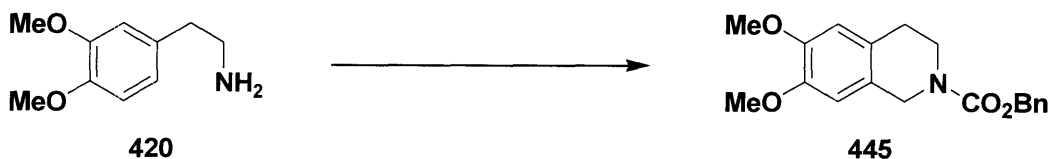




***N*-(Methoxycarbonyl)-6,7-dimethoxy-1-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline (444).**

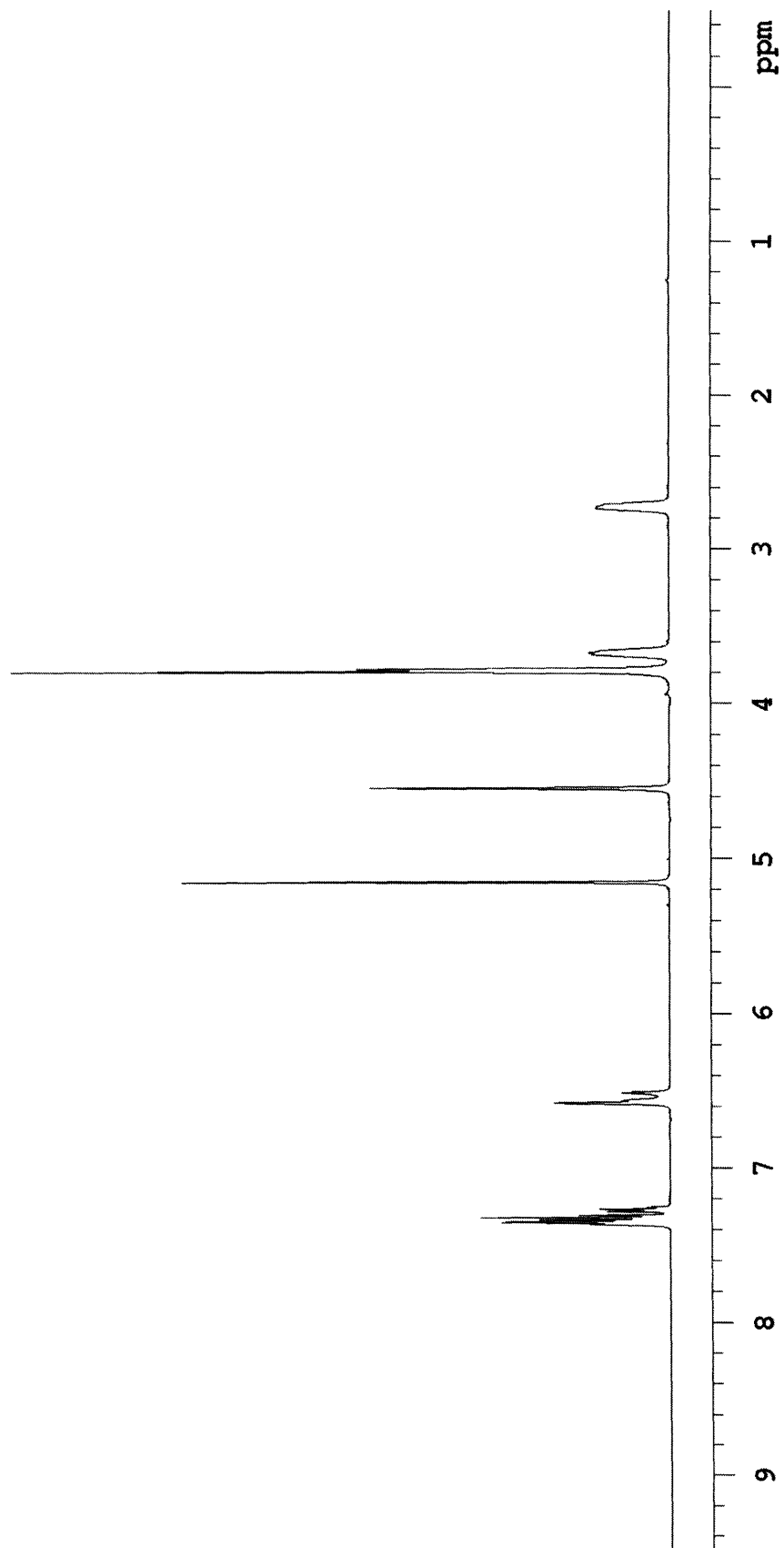
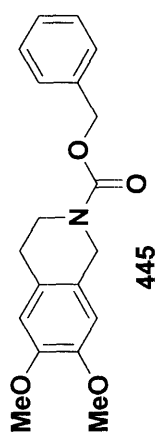
Reaction of amine **420** (2.1 mL, 2.3 g, 13 mmol), DMC (2.1 mL, 2.2 g, 25 mmol), methyl dimethoxyacetate (2.3 mL, 2.5 g, 19 mmol) and H₂SO₄ (2.0 mL, 9.0 M in H₂O, 18 mmol) according to General Procedure A afforded 2.910 g of a dark red oil. Column chromatography on 140 g of silica gel (gradient elution with 30–35% EtOAc-hexanes) provided 1.901 g (49%) of tetrahydroisoquinoline **444** as a colorless oil: IR (neat) 2954, 1744, 1699, 1611, 1520, and 1447 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.98 (rotamer, s, 0.5H), 6.96 (rotamer, s, 0.5H), 6.62 (s, 1H), 5.54 (rotamer, s, 0.5H), 5.47 (rotamer, s, 0.5H), 4.00 (rotamer, dt, *J* = 12.5, 5.5 Hz, 0.5H), 3.87 (s, 3H), 3.85 (s, 3H), 3.80 (rotamer, m, 0.5H), 3.76 (rotamer, s, 1.5H), 3.75 (rotamer, m, 0.5H), 3.74 (rotamer, s, 1.5H), 3.72 (rotamer, s, 1.5H), 3.71 (rotamer, s, 1.5H), 3.67 (rotamer, m, 0.5H), and 2.76–2.86 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 171.8, 156.0 (and rotamer 156.6), 148.66 (and rotamer 148.70), 147.66 (and rotamer 147.69), 127.3 (and rotamer 127.5), 121.6 (and rotamer 122.1), 111.0 (and rotamer 111.2), 110.6 (and rotamer 110.8), 57.5 (and rotamer 57.6), 56.1, 55.9, 53.0 (and rotamer 53.1), 52.56 (and rotamer 52.59), 40.2 (and rotamer 40.5), and 28.0 (and 28.2); GC-MS *m/z*: 309 (M⁺).

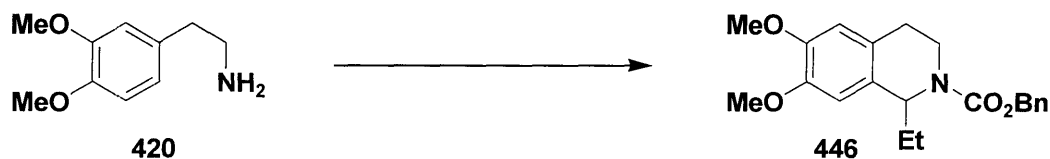




General Procedure B for the Two-Stage Reaction Using Trifluoroacetic Acid to Promote Pictet-Spengler Cyclization. *N*-(Carbobenzyloxy)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (445**).**

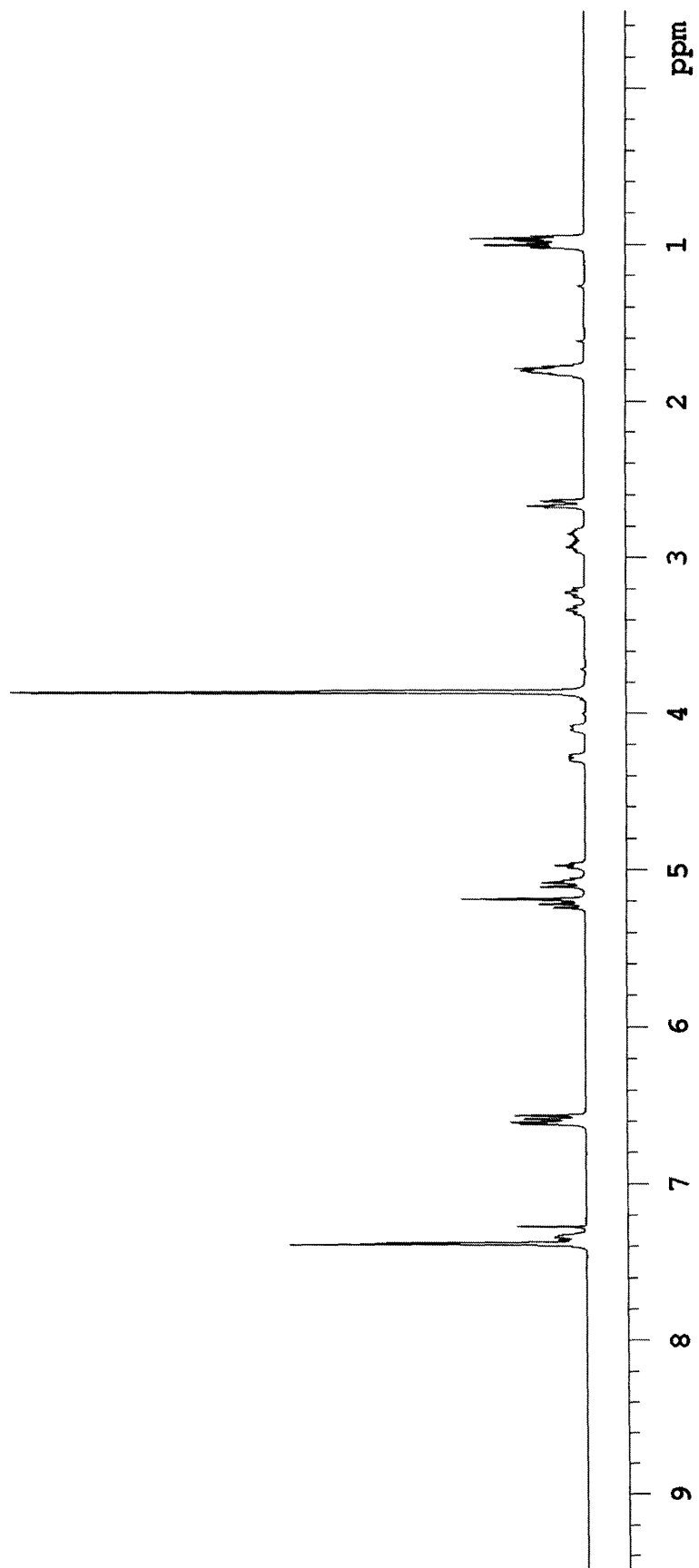
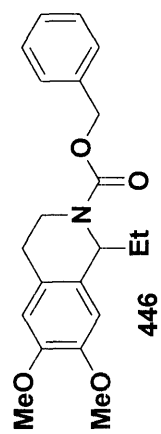
A 25-mL, stainless steel Thar view cell reactor was charged with amine **420** (2.1 mL, 2.3 g, 13 mmol) and dibenzyl carbonate (5.3 mL, 6.2 g, 26 mmol), pressurized to 50 bar with CO₂, heated to 130 °C, and then pressurized with additional CO₂ to 120 bar. The biphasic reaction mixture was stirred at 130 °C (120–130 bar) for 24 h. The reactor was allowed to cool to 80 °C and formaldehyde (1.5 mL, 13 M in H₂O, 20 mmol) and trifluoroacetic acid (3.0 mL, 50% v/v in H₂O, 19 mmol) were added sequentially via the 3-mL sample loop (depicted in Figure 2 as #9). The resulting triphasic reaction mixture was stirred at 80 °C (140–160 bar) for 24 h. The reactor was cooled to rt, the CO₂-phase was sparged into a biphasic mixture containing 15 mL of CH₂Cl₂ and 15 mL of water, and the remaining reactor contents were dissolved in 100 mL of CH₂Cl₂ and 100 mL of water. The combined organic and aqueous layers were washed with 100 mL of 1 M NaOH solution, and the aqueous layer was separated and extracted with four 75-mL portions of CH₂Cl₂. The combined organic layers were washed with 200 mL of satd NaCl solution, dried over MgSO₄, filtered, and concentrated to afford 8.528 g of a dark yellow oil. Column chromatography on 160 g of silica gel (gradient elution with 20–30% EtOAc-hexanes) provided 2.755 g (67%) of tetrahydroisoquinoline **445** as a colorless oil: IR (neat) 2935, 1703, 1692, 1611, 1517, and 1427 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.25–7.36 (m, 5H), 6.58 (s, 1H), 6.56 (rotamer, br s, 0.5H), 6.51 (rotamer, br s, 0.5H), 5.15 (s, 2H), 4.54 (s, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.67 (m, 2H), and 2.72 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 155.1 (and rotamer 155.2), 147.42, 147.37, 136.5, 128.3, 127.8, 127.6, 125.9 (and rotamer 126.1), 124.4 (and rotamer 125.0), 111.2 (and rotamer 111.3), 108.7 (and rotamer 108.9), 66.8 (and rotamer 66.9), 55.64, 55.63, 45.1 (and rotamer 45.3), 41.2 (and rotamer 41.5), and 28.0 (and rotamer 28.2); HRMS-ESI *m/z*: [M+Na]⁺ calcd for C₁₉H₂₁NO₄, 350.1363; found, 350.1360.

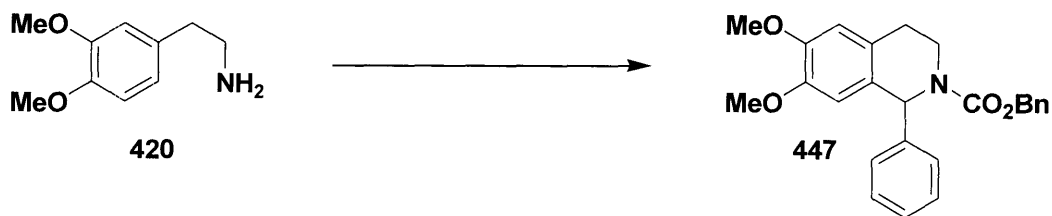




***N*-(Carbobenzyloxy)-1-ethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (446).**

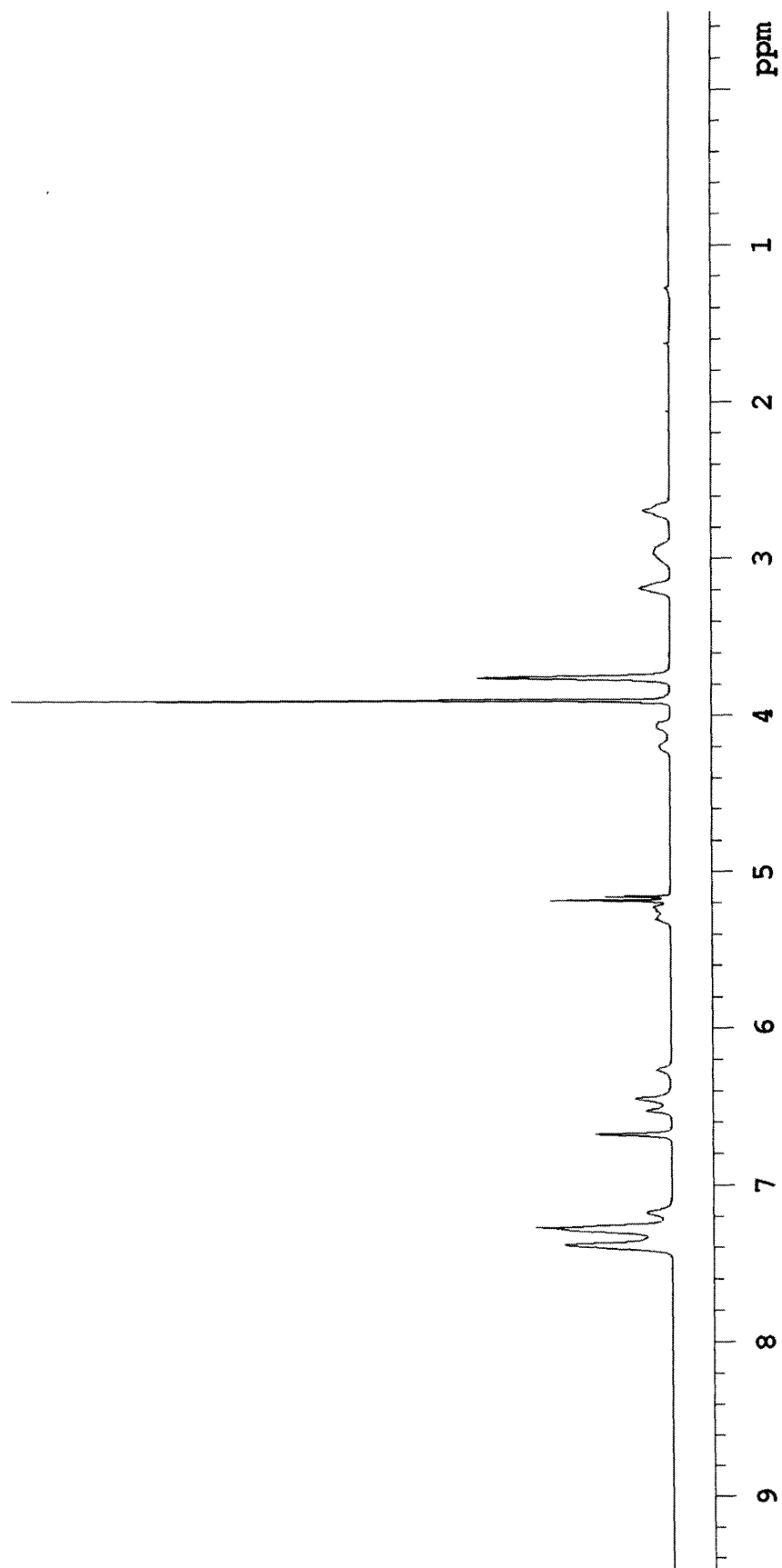
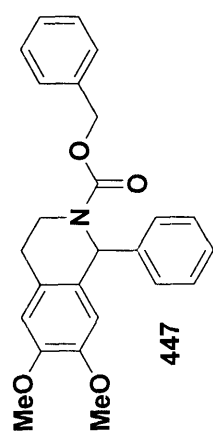
Reaction of amine **420** (2.1 mL, 2.3 g, 13 mmol), DBC (5.3 mL, 6.2 g, 26 mmol), propionaldehyde (1.4 mL, 1.1 g, 19 mmol) and TFA (3.0 mL, 50% v/v in H₂O, 19 mmol) according to General Procedure B afforded 8.890 g of an orange oil. Column chromatography on 140 g of silica gel (gradient elution with 10–30% EtOAc-hexanes) provided 3.173 g (71%) of tetrahydroisoquinoline **446** as a colorless oil: IR (neat) 2963, 1693, 1611, 1519, and 1427 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.33–7.38 (m, 5H), 6.62 (rotamer, s, 0.5H), 6.60 (rotamer, s, 0.5H), 6.58 (rotamer, s, 0.5H), 6.56 (rotamer, s, 0.5H), 5.23 (rotamer, d, *J* = 12.5 Hz, 0.5H), 5.18 (rotamer, s, 1H), 5.09 (rotamer, d, *J* = 12.5 Hz, 0.5H), 5.07 (rotamer, t, *J* = 7.3 Hz, 0.5H), 4.97 (rotamer, t, *J* = 7.3 Hz, 0.5H), 4.28 (rotamer, m, 0.5H), 4.09 (rotamer, m, 0.5H), 3.86 (s, 6H), 3.33 (rotamer, m, 0.5H), 3.22 (rotamer, m, 0.5H), 2.93 (rotamer, m, 0.5H), 2.85 (rotamer, m, 0.5H), 2.67 (rotamer, m, 0.5H), 2.64 (rotamer, m, 0.5H), 1.80 (m, 2H), 1.00 (rotamer, t, *J* = 7.3 Hz, 1.5H), and 0.96 (rotamer, t, *J* = 7.3 Hz, 1.5H); ¹³C NMR (125 MHz, CDCl₃) δ 155.2, 147.2 (and rotamer 147.3), 147.0, 136.4 (and rotamer 136.6), 129.2 (and rotamer 129.5), 128.0, 127.48 (and rotamer 127.6), 127.3 (and rotamer 127.55), 125.3 (and rotamer 125.5), 111.0 (and rotamer 111.2), 109.5 (and rotamer 109.8), 66.5 (and rotamer 66.8), 55.5, 55.4, 55.3, 37.0 (and rotamer 37.7), 29.2 (and rotamer 29.4), 27.4 (and rotamer 27.8), and 10.68 (and rotamer 10.72); HRMS-ESI *m/z*: [M+Na]⁺ calcd for C₂₁H₂₅NO₄, 378.1676; found, 378.1666.

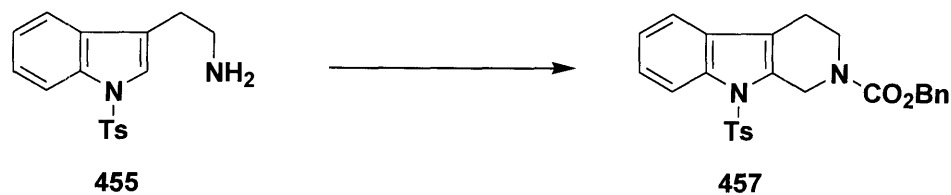




***N*-(Carbobenzyloxy)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (447).**

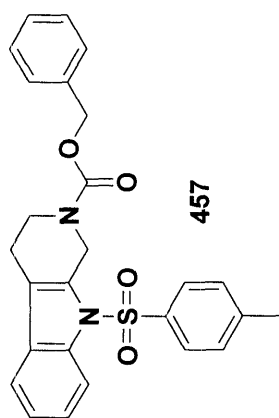
Reaction of amine **420** (2.1 mL, 2.3 g, 13 mmol), DBC (5.3 mL, 6.2 g, 26 mmol), benzaldehyde (2.0 mL, 2.1 g, 18 mmol) and H₂SO₄ (2.0 mL, 9.0 M in H₂O, 18 mmol) according to General Procedure A afforded 8.960 g of an orange oil. Column chromatography on 100 g of silica gel (gradient elution with 5–30% EtOAc-hexanes) provided 2.882 g (57%) of tetrahydroisoquinoline **447** as a very pale yellow oil: IR (neat) 2935, 1693, 1611, 1517, and 1425 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.17–7.40 (m, 10H), 6.68 (s, 1H), 6.53 (s, 1H), 6.45 (rotamer, br s, 0.5H), 6.26 (rotamer, br s, 0.5H), 5.22–5.30 (m, 1H), 5.18 (rotamer, s, 0.5H), 5.16 (rotamer, s, 0.5H), 4.20 (rotamer, br s, 0.5H), 4.07 (rotamer, br s, 0.5H), 3.90 (s, 3H), 3.76 (s, 3H), 3.19 (br s, 1H), 2.96 (br s, 1H), and 2.69 (br s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 154.9 (and rotamer 155.3), 147.9, 147.4, 142.4, 136.6, 128.5, 128.4, 128.3, 128.2, 127.7 (and rotamer 127.9), 127.4, 127.0, 126.7 (and rotamer 126.8), 126.6, 110.9 (and rotamer 111.2), 67.1 (and rotamer 67.4), 57.1 (and rotamer 57.3), 55.8, 55.7, 37.6 (and rotamer 37.8), and 27.8 (and rotamer 28.0); HRMS-ESI *m/z*: [M+Na]⁺ calcd for C₂₅H₂₅NO₄, 426.1676; found, 426.1683.



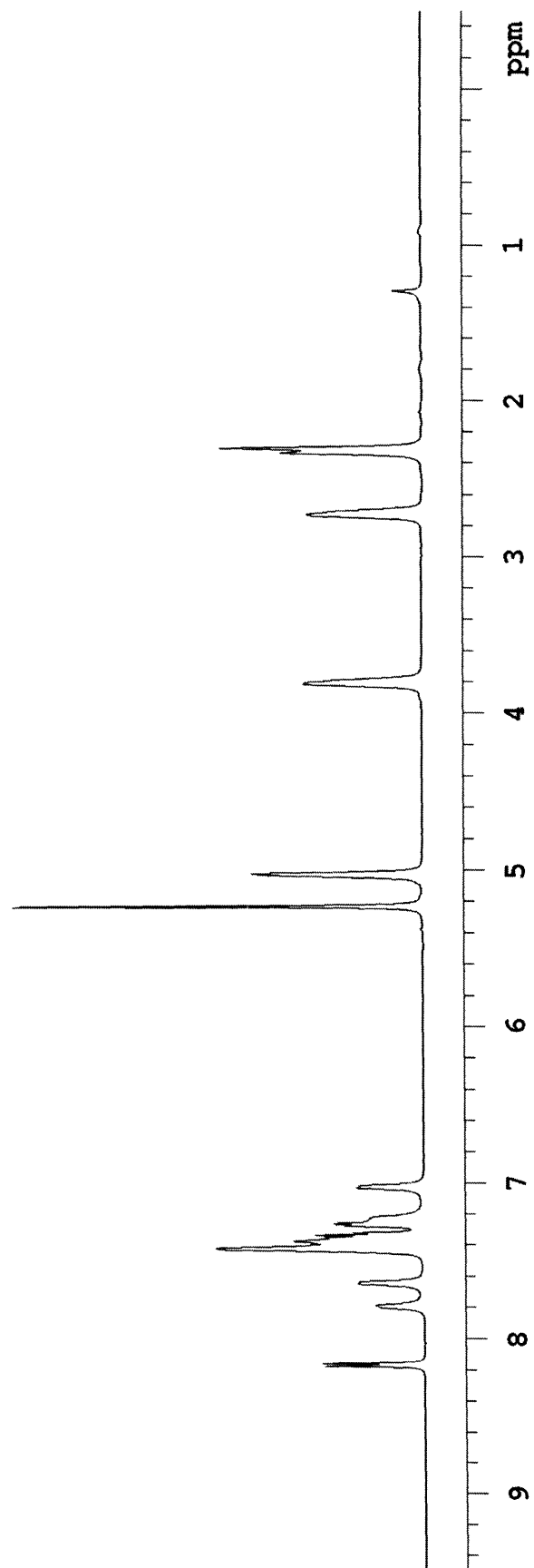


2-(Carbobenzyloxy)-9-(*p*-toluenesulfonyl)-1,2,3,4-tetrahydro- β -carboline (457).

A 25-mL, stainless steel Thar view cell reactor was charged with tryptamine **455** (0.798 g, 2.54 mmol) and DBC (2.7 mL, 3.2 g, 13 mmol), pressurized to 50 bar with CO₂, heated to 130 °C, and then pressurized with additional CO₂ to 130 bar. The biphasic reaction mixture was stirred at 130 °C (130 bar) for 24 h. The reactor was allowed to cool to 80 °C and formaldehyde (0.50 mL, 6.8 M in H₂O, 3.4 mmol) and TFA (0.50 mL, 50% v/v in H₂O, 3.2 mmol) were added sequentially via the 0.50-mL sample loop (depicted in Figure 2 as #9). The resulting triphasic reaction mixture was stirred at 80 °C (160 bar) for 24 h. The reactor was cooled to rt, the CO₂-phase was sparged into a biphasic mixture containing 15 mL of CH₂Cl₂ and 15 mL of water, and the remaining reactor contents were dissolved in 100 mL of CH₂Cl₂ and 50 mL of water. The combined organic and aqueous layers were washed with 50 mL of satd NaHCO₃ solution, and the aqueous layer was separated and extracted with three 50-mL portions of CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered, and concentrated to afford 4.116 g of a yellow oil. Two successive purifications by column chromatography on 120 g of silica gel (5–20% EtOAc-hexanes) provided 0.715 g (61%) of tetrahydro- β -carboline **457** as a white solid: mp 52–55 °C; IR (film) 2922, 1704, 1597, 1426, 1366, and 1232 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.16 (d, *J* = 8.2 Hz, 1H), 7.79 (m, 1H), 7.64 (m, 1H), 7.32–7.44 (m, 7H), 7.21–7.28 (m, 2H), 7.02 (m, 1H), 5.23 (s, 2H), 5.02 (br s, 2H), 3.81 (br s, 2H), 2.73 (br s, 2H), 2.33 (rotamer, s, 1H), and 2.30 (rotamer, s, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 155.6 (and rotamer 155.7), 145.1, 136.7, 135.5 (and rotamer 136.2), 131.0 (and rotamer 131.6), 130.1, 129.6, 128.7, 128.3, 128.1, 126.5 (and rotamer 126.7), 124.7 (and rotamer 124.8), 123.6 (and rotamer 123.7), 118.4 (and rotamer 118.5), 117.1 (and rotamer 117.8), 114.4, 67.6, 43.5 (and rotamer 43.8), 41.2 (and rotamer 41.4), 21.7, and 21.2; HRMS-ESI *m/z*: [M+Na]⁺ calcd for C₂₆H₂₄N₂O₄S, 483.1349; found, 483.1355.



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Joshua R. Dunetz

Education

- 2000-2005 **Massachusetts Institute of Technology**
Ph.D., Organic Chemistry, received September 2005
Thesis: "I. Synthesis of Indolines and Indoles via Intramolecular [4 + 2] Cycloaddition of Ynamides and Conjugated Enynes. II. Synthesis of Nitrogen Heterocycles in Supercritical Carbon Dioxide"
Advisor: Professor Rick L. Danheiser
- 1996-2000 **Haverford College**
Graduated *magna cum laude* in May 2000
B.A., Chemistry (High Honors) with Biochemistry concentration
Thesis: "The *de novo* Synthesis of Light Harvesting Peptides"
Advisor: Professor Karin S. Åkerfeldt

Research Experience

- 2000-2005 **Graduate Research Assistant, Massachusetts Institute of Technology**
Advisor: Professor Rick L. Danheiser
- Designed and developed a general method for the synthesis of ynamides
 - Developed new intramolecular [4 + 2] cycloadditions of ynamides and conjugated enynes as a convergent route to substituted indolines and indoles
 - Designed and developed a method for conducting Pictet-Spengler cyclizations in supercritical carbon dioxide
- 1999-2000 **Research Assistant, Haverford College**
Advisor: Professor Karin S. Åkerfeldt
- Designed and synthesized porphyrin-peptides as models for biochemical energy transfer
 - Studied molecular modeling and *ab initio* computational techniques
- Summers
1998, 1999 **Research Assistant, Kennedy Krieger Institute at Johns Hopkins Hospital**
Advisor: Dr. Michael V. Johnston
- Examined the effects of hypoxia on prenatal brain cells
- Summer
1998 **Summer Research Fellowship, Haverford College**
Advisor: Professor Frances R. Blase
- Conducted studies toward the synthesis of the lactone ring of discodermolide from glucose

Teaching Experience

- 2002-2005 **Chemistry Outreach Program, Massachusetts Institute of Technology**
- Visited local high schools to present exciting and educational chemistry demonstrations

- 2003, 2000-2001 **Teaching Assistant, Massachusetts Institute of Technology**
- Taught recitation sections for two semesters of introductory organic chemistry, prepared lesson plans, held review sessions, and graded problem sets and exams
 - Assisted with a graduate class on advanced organic synthesis
- 1998-2000 **Lab Assistant and Tutor, Haverford College**
- Prepared experiments for introductory organic chemistry laboratories
 - Tutored introductory organic chemistry

Honors and Awards

- 2004 Cambridge Science Foundation travel grant
- 2001 MIT Outstanding Teaching Assistant Award
- 2000 American Institute of Chemists Award
- 2000 Outstanding Poster Presentation (AAAS meeting, Feb 2000, Physical Chemistry Division)
- 1999 Merck-AAAS Scholars undergraduate research fellowship
- 1998 Howard Hughes Medical Institute undergraduate research fellowship

Affiliations

- Phi Beta Kappa Honor Society, member since 2000
- American Chemical Society, Organic Division, member since 2001

Publications

- Kohnen, A. L.; Dunetz, J. R.; Danheiser, R. L. Synthesis of Ynamides by N-Alkynylation of Amine Derivatives. In preparation – invited by Organic Synthesis.
- Gould, A. E.; Palucki, B. L.; de la Pradilla, R. F.; Helgason, A. L.; Yli-Kauhaluoma, J.; Hayes, M. E.; Dunetz, J. R.; Danheiser, R. L. Intramolecular [4 + 2] Cycloadditions of Conjugated Enynes. Scope and Mechanism of Thermal Cycloadditions. In preparation.
- Dunetz, J. R.; Ciccolini, R. P.; Fröling, M.; Paap, S. M.; Allen, A. J.; Holmes, A. B.; Tester, J. W.; Danheiser, R. L. Pictet-Spengler Reactions in Multiphasic Supercritical Carbon Dioxide / CO₂-Expanded Liquid Media. In Situ Generation of Carbamates as a Strategy for Reactions of Amines in Supercritical Carbon Dioxide. *Chem. Commun.* **2005**, 4465.
- Dunetz, J. R.; Sandstrom, C.; Young, E. R.; Baker, P.; Van Name, S. A. Cathopolous, T.; Fairman, R.; de Paula, J. C.; Åkerfeldt, K. S. Self-Assembling Porphyrin-Modified Peptides. *Org. Lett.* **2005**, 7, 2559.
- Dunetz, J. R.; Danheiser, R. L. Synthesis of Highly Substituted Indolines and Indoles via Intramolecular [4 + 2] Cycloaddition of Ynamides and Conjugated Enynes. *J. Am. Chem. Soc.* **2005**, 127, 5776.
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Presentations

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